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Interventions for the control of diarrhoeal diseases among young children: supplementary feeding programmes

R.G. FEACHEM[1]

The effect of supplementary feeding programmes on diarrhoeal disease morbidity and mortality among preschool children is reviewed using data from field studies in developing countries. The supplementary feeding programmes considered are those that provide food to preschool children on a continuing and community-wide basis. Nutritional rehabilitation of sick children and feeding programmes in disasters and emergencies are not considered. The evidence that poor nutritional status predisposes to increased diarrhoeal disease incidence, or that supplementary feeding programmes can reduce diarrhoeal disease incidence, is not strong. There is evidence that poor nutritional status predisposes to more severe diarrhoea and to higher case fatality, and that supplementary feeding programmes can reduce the severity of the diarrhoea and the mortality. However, supplementary feeding programmes entail high costs and considerable logistic and managerial complexity and it is unlikely that they are a cost-effective intervention for national diarrhoeal diseases control programmes. Prospective studies into the effect of nutritional status on the severity of etiology-specific diarrhoeas and the resulting deaths are warranted.

A synergism between diarrhoeal diseases and nutritional status has been accepted for many years (*35*) and substantial research efforts have been directed towards unravelling the nature of this synergism. Some authorities (*41*) have suggested that the enhancement of nutritional status by supplementary feeding programmes may be an effective intervention to reduce the rates of diarrhoeal diseases in preschool children. Supplementary feeding programmes refer here to the planned distribution of foodstuffs to improve the dietary intake of preschool children (6 months to 5–6 years is the usual age range of target children). The food distribution may be on a 'take-home' basis or it may involve supervised feeding at feeding centres. Supplementary feeding programmes may aim to reach the whole of a stated age–sex group, or they may be targeted at children with particular levels of nutritional deprivation. Several recent reviews of supplementary feeding programmes provide a useful background to this more focused analysis (*1*, *8*, *20*, *23*). The therapeutic feeding, over short periods, of children suffering from severe malnutrition and diarrhoea is undoubtedly an essential part of case management and can reduce the case fatality rate among such children. In this review, however, such nutritional rehabilitation of sick children is not considered and only data on the preventive effect of more broadly targeted supplementary feeding programmes are considered. This review of the role of supplementary feeding programmes in diarrhoeal disease control is the second in a series of reviews of potential anti-diarrhoea interventions being published in the *Bulletin of the World Health Organization* (*15*, *16*).

[1] Reader in Tropical Public Health Engineering and Head of Department of Tropical Hygiene, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, England. Requests for reprints should be addressed to the Programme Manager, Diarrhoeal Diseases Control Programme, World Health Organization, 1211 Geneva 27, Switzerland.

EFFECTIVENESS

For supplementary feeding programmes to be an effective diarrhoea control intervention, it must be true that:

either

supplementary feeding programmes can improve the nutritional status of young children	*hypothesis 1*

and

young children with improved nutritional status have reduced diarrhoea morbidity rates and/or mortality rates and/or severity	*hypothesis 2*

or

supplementary feeding programmes can reduce diarrhoea morbidity rates and/or mortality rates and/or severity in young children	*hypothesis 3*

Most of the literature on this topic has been addressed to one or more of these specific hypotheses. The potential effectiveness of supplementary feeding programmes would be suggested by a demonstration either of the correctness of hypotheses 1 and 2 or of the correctness of hypothesis 3. The evidence for and against the three hypotheses is now examined.

Hypothesis 1. *Supplementary feeding programmes can improve the nutritional status of young children*

Beaton & Ghassemi (*8*) reviewed the impact on nutritional status of 43 supplementary feeding programmes. Major differences in the nature and goals of the feeding programmes, and in the methods for evaluating their impact, make it difficult to draw generalized conclusions from these programmes (*7*). There is no doubt that supplementary feeding programmes can have a major impact on the nutritional status of individual participating children, and that the worse the initial nutritional state of the child, the greater is the improvement in anthropometric indices that may be attributed to the feeding programme. Impact on the nutritional status of the target group as a whole, however, is typically low or non-existent. This lack of impact may be due to the following factors:

(i) *Low coverage*: a considerable proportion (20–75%) of children enrolled in supplementary feeding programmes fail to participate, while many more children in the region or country are denied access because of limitations in the programme infrastructure. Coverage in programmes reviewed by Beaton & Ghassemi was typically less than 10%.

(ii) *Low levels of supplementation*: in programmes reviewed by Beaton & Ghassemi, the supplementation was designed to meet 40–70% of the estimated energy gap, but in practice only 10–25% of the gap was closed. Energy intakes from supplementary food ranged from 19 to 431 kcal (79.5 to 1803 kJ) per child per day.

(iii) *Food sharing*: in take-home feeding programmes, only 40–60% of the food distributed appeared to reach the targeted children, the remainder being consumed by other family members or being sold (*8*).

(iv) *Food substitution*: there is often a compensatory decrease in the intake of other foods. In 5 out of 7 programmes reviewed by Beaton & Ghassemi in this regard, the net increase in energy intake among the participating children, as a percentage of the energy in the supplementary food ingested, was less than 100% and in one programme it was as low as 16%.

Many of the feeding programmes reviewed by Beaton & Ghassemi (*8*) were research or pilot interventions rather than routine feeding programmes, and the former tend to have greater impact than the latter. Some of the research interventions, for instance in Colombia, Guatemala and India, produced mean weight gains in project children that were 0.5–1.0 kg/year greater than in the control children. These marked impacts in research interventions may serve to define maximum impacts, but they do not reflect the generally more modest achievements of routine supplementary feeding programmes.

The programmes reviewed were, in general, not effective in reaching children aged 6–23 months. This is probably due to traditional practices of late weaning and to maternal attitudes towards appropriate feeding regimens for children of this age. Since diarrhoea rates are at their highest in this 6–23-month period (*36*), this finding is important in the context of diarrhoea control and suggests that attention may be better directed towards improved weaning practices than supplementary feeding programmes.

Hypothesis 2. *Young children with improved nutritional status have reduced diarrhoeal morbidity rates and/or mortality rates and/or severity.*

Associations have been frequently reported between poor nutritional status and increased diarrhoea morbidity, mortality, and severity. This literature is comprehensively reviewed by Leslie.[a] These associ-

[a] LESLIE, J. *Child malnutrition and diarrhea: a longitudinal study from north-east Brazil.* Doctor of Science thesis, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, MD, USA, 1982.

ations could be due to one or more of the following:

— diarrhoea causes poor nutritional status (proposition 1);

— poor nutritional status predisposes to diarrhoea (proposition 2);

— both poor nutritional status and diarrhoea are associated with other factors such as a recent measles attack or poverty (proposition 3).

The evidence for the first proposition (diarrhoea causes poor nutritional status) is considerable (*14*, *28*, *29*, *32*).[b] This implies that diarrhoea control may be an effective anti-malnutrition intervention. The third proposition is also true, it being well established that both diarrhoea and poor nutritional status are found disproportionately among the deprived and underprivileged sections of the community (*40*). The precise cause-and-effect relationships are not understood but the general conclusion is that overall socioeconomic development may gradually reduce both diarrhoea and malnutrition. For the second proposition (poor nutritional status predisposes to diarrhoea) there is uncertainty and controversy. It is only if this proposition is correct that nutritional supplementation could be an effective anti-diarrhoea intervention.

Most studies into the association between diarrhoea and nutrition have failed to separate proposition 1 from proposition 2, and have also failed to allow for the confounding variables of proposition 3. Only a few prospective studies have adequately explored proposition 2. The study by Chen et al. (*13*) in rural Bangladesh is summarized in Table 1, in which the first finding is typical of many previous studies and fails to disentangle propositions 1 and 2 or to control for confounding variables; the remaining findings are of greater interest and fail to show that poor nutritional status predisposes to increased incidence of diarrhoeal illness.

Another prospective study was that of 343 children aged 6–32 months in rural northern Nigeria (*38*). The heights and weights of each child were recorded in April and the incidence and duration of diarrhoea were recorded during May–July by weekly home visits. The period May–July coincides with the end of the dry season and the start of the rains and is the period of peak diarrhoea incidence. The results of this study are shown in Table 2. Being underweight or

[b] See footnote *a*, page 968.

Table 1. Association between nutritional status and diarrhoea incidence in rural Bangladesh[a]

Type of data collected	Finding
1. Discharge weight-for-age of 811 children (0–4 years) treated for diarrhoea at rural hospital compared with weight-for-age of 882 children of the same age range in the community.	For both males and females the prevalence of severely malnourished children (< 60% weight-for-age) was significantly higher among diarrhoea cases than among village children.
2. Diarrhoea treatment rate over 2 years for 2019 children (12–23 months) according to nutritional status (weight-for-age, weight-for-height, height-for-age) at the start of the 2-year period.	No association was found between nutritional status and diarrhoea treatment rate, either for individual anthropometric measures or combined measures.
3. Diarrhoea incidence by community surveillance over 1 year among 207 children (0–4 years) according to nutritional status (weight-for-age) at the start of 1 year's surveillance.	No association was found between nutritional status and diarrhoea incidence rate.
4. Probability of experiencing diarrhoea in a given 4-week period among 207 children (0–4 years) according to weight gain (weight-for-age % increase, body weight % increase, body weight kg increase) in previous 4-week period.	No association was found between weight gain and probability of diarrhoea.

[a] Summary of Chen et al. (*13*).

Table 2. Association between nutritional status and diarrhoea incidence and duration among children aged 6–32 months in rural northern Nigeria[a]

Nutritional status	No. of children	Diarrhoea attack rate per child over 3 months[b]	Time with diarrhoea (%)[b]
Weight/age:			
> 75%	220	1.25	8.5 } **
< 75% (underweight)	123	1.52	11.3 } **
Height/age:			
> 90%	245	1.37	7.9 } **
< 90% (stunting)	98	1.45	10.8 } **
Weight/height:			
> 80%	302	1.29 } *	7.6 } ***
< 80% (wasting)	41	1.90 } *	13.8 } ***

[a] Data from Tomkins (*38*).

[b] Significance values of comparisons within anthropometric groups: $^{*}P < 0.02$; $^{**}P < 0.01$; $^{***}P < 0.001$.

stunted did not predispose to increased diarrhoea incidence but being wasted was associated with a significantly higher attack rate. Being underweight, or stunted or wasted were all associated with a significantly increased duration of diarrhoea, and this effect was most marked for children who were wasted. The major defect of this study is that socioeconomic and environmental variables were not controlled. It could be that children who were undernourished in April tended to come from more crowded, less educated, poorer and dirtier homes than other children (*40*). Such disadvantaged children might experience increased exposure to diarrhoea-causing organisms (and thus higher attack rates) and receive less adequate care when sick (and thus have a longer duration of illness) than other children. The Nigerian report (*38*) provides no data on the degree of familial clustering of the children with poor nutritional status. Since the confounding variables mentioned above are all family attributes, future studies of this type should control for familial variation, perhaps by comparing poorly nourished children with well nourished children in the same families. Trowbridge et al. (*39*) found a strong association between poor nutritional status and diarrhoea incidence in the subsequent 12 months in El Salvador, but recognized that this association could be confounded by socioeconomic status.

Other studies have recorded a relationship between poor nutritional status and increased duration of diarrhoea. Palmer et al. (*30*) found increased cholera duration among hospitalized male Bangladeshis of low weight-for-height, although, since anthropometric measures were made at discharge, it was not clear whether the low weight caused prolonged cholera or vice versa. In a prospective study in San José, Costa Rica, the average duration of diarrhoea episodes in children aged 12–59 months was significantly longer among those with low weight-for-age than among others (*22*).

Two studies of children admitted to hospital with acute diarrhoea of known etiology in Bangladesh failed to find an association of poor nutritional status with diarrhoea duration, but did find an association with diarrhoea severity as measured by the rate of stool output and degree of dehydration. In the first study (*10*), which was of children with rotavirus diarrhoea, those with low (< 60%) weight-for-age had a higher frequency of severe dehydration, but a similar duration of diarrhoea, than others. In the second study,[c] no difference was found in the rate of stool output, total stool volume, or diarrhoea duration between children of poor (< 80% weight-for-height) and better (⩾ 80% weight-for-height) nutritional status who had been admitted to hospital with acute rotavirus or enterotoxigenic *Escherichia coli* diarrhoea. However, the rate of stool output (per kg of body weight) was significantly higher among children with small body size (low weight- and height-for-age).

If poor nutritional status predisposes to more severe diarrhoea, particularly in the form of more dehydrating diarrhoea or diarrhoea of longer duration, then it would be expected that poor nutritional status would predispose to diarrhoea mortality. Chen et al. (*11*) measured the heights and weights of 2019 children aged 12–23 months in rural Bangladesh and then recorded mortality among these children over the following 2 years. A striking association between nutritional status (weight-for-age) and subsequent diarrhoea mortality was recorded (Table 3), with children < 65% weight-for-age having a diarrhoea mortality rate 3.8 times higher than children ⩾ 65% weight-for-age. In this and another report (*12*) a marked association between mortality rate and socioeconomic status (measured by housing floor area) in the same children was noted. Unfortunately the data on diarrhoea mortality by nutritional status are not controlled for socioeconomic status and the possible importance of this confounding variable is not elucidated.

Other prospective studies have also reported an association between poor nutrition and diarrhoea mortality. In rural Punjab, India, 71% of under-3-year-old children dying from diarrhoea were < 70% weight-for-age in the two months preceding death (*27*). The mean prevalence of < 70% weight-for-age in children from the same community at the same time was significantly lower (25%). In rural Bangladesh, children aged 0–9 years who died of diarrhoea had a pre-morbid mean weight-for-height of 74% of the standard, compared with 83–86% of standard for children who died of other causes and 88% of standard for living controls (*26*).

In summary, the evidence that poor nutritional status predisposes to increased diarrhoea incidence is

Table 3. Association between nutritional status and diarrhoea mortality among children aged 12–23 months (at start of study) in rural Bangladesh[a]

Nutritional status (weight-for-age)	No. of children	Diarrhoea mortality per 1000 over 2 years
All children	2019	20
Children < 65%	742	38
Children ⩾ 65%	1277	10

[a] Data from Chen et al. (*11*).

[c] BLACK, R. E. ET AL. Nutritional status, body size and severity of diarrhoea associated with rotavirus or enterotoxigenic *Escherichia coli*. (Unpublished).

not strong. There is good evidence, however, that children with poor nutritional status are more likely to have dehydrating or prolonged diarrhoea, and are more likely to die from diarrhoea, than well nourished children. Data from Bangladesh suggest that children < 65% weight-for-age have a diarrhoea mortality rate 3.8 times higher than other children (*11*). There is a need for more studies to clarify further the association between poor nutritonal status and risk of severe diarrhoea and diarrhoea death. Such studies should be etiology-specific and prospective, and control for family socioeconomic status. No studies so far reported meet these three criteria and very little is known of the possible differing effects of nutritional status on diarrhoeas of differing etiology.

Hypothesis 3. *Supplementary feeding programmes can reduce diarrhoea morbidity rates and/or mortality rates and/or severity in young children*

Only a small minority of supplementary feeding programmes collect data on their impacts, and only a minority of these evaluate impact by measuring the changes in mortality or morbidity. Annex 1 summarizes the results of evaluations of 9 supplementary feeding programmes, which included measurement of mortality and/or morbidity changes. Of the 9 programmes, 6 investigated mortality changes and, of these, 5 found that mortality was reduced while 1 found that it was not. Of the 5 programmes with a mortality reduction, 2 included both nutritional supplementation and curative health care and it is not possible to separate out the impact of the nutritional intervention alone. Three studies (in Guatemala in 1959–64; in Punjab, India; and in Peru) documented a significant reduction in mortality that was attributed to supplementary feeding alone, but no data are presented on the impact on diarrhoea mortality specifically. It is reasonable to assume that the percentage reduction in diarrhoea mortality is at least as great as the reduction in mortality from all causes. With this assumption, the reduction in diarrhoea mortality due to the supplementary feeding programmes in Guatemala and the Punjab may have been 19–31% among children under 1 year of age and around 50% among children aged 1–4 years. In Peru there was a striking (> 50%) reduction in diarrhoea mortality among infants under 1 year of age.

Theoretical reductions in diarrhoea mortality achieved by a supplementary feeding programme may be computed (Table 4). Six different initial prevalences of severe malnutrition are considered and supplementary feeding programmes are assumed to either eliminate severe malnutrition or to cut its prevalence by half. Reductions in diarrhoea mortality are then computed by assuming that severely malnourished children have a diarrhoea mortality rate 3.8 times higher than other children and that only severely malnourished children are predisposed to diarrhoea mortality (*11*). The reductions in diarrhoea mortality thus estimated are in the range 6–46% and are greater in communities with a higher prevalence of severe malnutrition. These calculations are greatly simplified and take no account of age-related effects. Children aged under 2 years have the highest diarrhoea mortality rate (*36*) but are least affected by supplementary feeding programmes. The relative risk of diarrhoea mortality for severely malnourished children (3.8) was taken from a single study in Bangladesh of children between 12 and 47 months of age. Table 4 can be recomputed with respect to a particular community in which the prevalence of severe malnutrition and the differential diarrhoea mortality rates of severely malnourished children are known.

Table 4. Estimated reductions in diarrhoea mortality among children under 5 years of age due to supplementary feeding programmes of differing effectiveness in communities with differing levels of severe malnutrition

% of children < 65% weight-for-age		% reduction in diarrhoea mortality rate caused by nutritional intervention[a]
before nutritional intervention	after nutritional intervention	
5	0	12
5	2.5	6
10	0	22
10	5	11
15	0	30
15	7.5	15
20	0	36
20	10	18
25	0	41
25	12.5	21
30	0	46
30	15	23

[a] Assuming that children < 65% weight-for-age have a 3.8 times higher diarrhoea mortality rate than other children (see Table 3).

Six of the 9 programmes were evaluated for their impact on diarrhoea incidence: 1 showed an impact, 3 showed no impact, and 2 could not be interpreted owing to deficient study methods. The one study that showed an impact on diarrhoea morbidity (in Madhya Pradesh, India) evaluated the combined

impact of supplementary feeding of 6–35-month-old children plus a comprehensive package of curative and preventive health care. The effect of the nutritional intervention alone cannot be determined. One study (in Guatemala, 1959–64) documented a reduced case-fatality ratio for diarrhoea (1.7% vs 0.8%) and a reduced proportion of severe diarrhoeas (20% vs 10%) that were attributed to the supplementary feeding intervention.

In summary, there is evidence from three studies and from theoretical calculations that supplementary feeding programmes can reduce diarrhoea mortality in children under 5 years of age. The magnitude of this reduction may be as high as 50% in some age groups and in communities where severe malnutrition is common. There is no evidence that supplementary feeding can reduce diarrhoea incidence, and some evidence that it can reduce the case-fatality ratio and the severity of diarrhoea episodes. These findings correspond closely to the conclusions on hypothesis 2.

FEASIBILITY

Supplementary feeding programmes have been implemented in many developed and developing countries. There is considerable accumulated operational experience of such programmes and this has been reviewed (*1*, *8*). The major operational difficulties are to attain and sustain a high coverage of targeted children and to ensure that the participating children regularly ingest a sufficient amount of supplementary energy. These and other difficulties are discussed above in the section dealing with hypothesis 1.

COSTS

The costs of operational supplementary feeding programmes reviewed by Beaton & Ghassemi (*8*) were US$ 23–39 (1982 dollars) per child enrolled per year. These costs were for the provision of 300–400 kcal (1255–1674 kJ) per child per day and include food plus delivery and administration. Total costs in supervised feeding programmes were somewhat higher than in take-home programmes. The cost of food accounted for about 70% of the total cost of take-home programmes. Since non-participation is common (20–75% of children enrolled fail to participate), the costs per participating child are increased by 1.25–4 times, thus giving a maximum cost range of US$ 29–156 (1982 dollars) per participating child per year.

In a review of CARE preschool feeding programmes in five countries, Anderson et al. (*1*) reported costs of US$ 21–147 (1982 dollars) per participating child. Food accounted for between 54% and 92% of these costs. When costs are computed not per participating child, but per malnourished child (judged nutritionally or anthropometrically), the figures increase considerably (Table 5).

If the annual cost per participating child is US$ 100 (Table 5), and if a 20% reduction in diarrhoea mortality is achieved among participating children (Table 4) having a pre-intervention annual diarrhoea mortality rate of 1.4 per 100 children (*36*), the cost per diarrhoea death averted is US$ 36 000. Under the most favourable conditions, with an annual cost per participating child of US$ 20 and a 50% diarrhoea mortality reduction achieved, the cost per diarrhoea death averted is US$ 2900. These calculations underestimate the cost-effectiveness of supplementary feeding programmes by assuming that they achieve no benefits other than prevention of diarrhoea mortality.

CONCLUSIONS

The evidence that poor nutritional status predisposes to increased diarrhoeal disease incidence, or that supplementary feeding programmes can reduce diarrhoeal disease incidence, is not strong. There is evidence that poor nutritional status predisposes to more severe diarrhoea and to higher case fatality, and

Table 5. Annual feeding programme costs in four countries[a]

Country	Annual cost (in 1982 US$) per participating child	per child with energy deficit	per child with anthropometric deficiency
Colombia			
take-home	39	45	406
Dominican Republic			
dry, take-home	21	23	103
wet, take-home	24	26	116
Pakistan			
take-home	37	45	71
Costa Rica			
on-site	147	175	452

[a] Data from Anderson et al. (*1*). Costs converted to 1982 US$ using GNP deflators computed from data in *International financial statistics*.

that supplementary feeding programmes can reduce diarrhoea severity and mortality.

Supplementary feeding programmes, however, entail high costs and considerable logistic and managerial complexity and have typically failed to achieve a significant improvement in the nutritional status of children aged 6–23 months, who have the highest rates of sickness and death from diarrhoea. It is unlikely that supplementary feeding programmes are a cost-effective intervention for national diarrhoeal diseases control programmes. Prospective studies into the effect of nutritional status on the severity of etiology-specific diarrhoeas and the resulting deaths (using the methods recommended above) are warranted.

Therapeutic feeding has not been included in this review. Such feeding can be life-saving for the severely malnourished child. Also not included are feeding programmes implemented in emergency or disaster situations where inadequate food availability may be the cause of malnutrition for a majority of children. Reviewed here are supplementary feeding programmes designed to enhance food intake of preschool children over several years and on a community-wide basis. Such programmes are shown to be costly, to be ineffective in reducing diarrhoea morbidity rates, and to be of uncertain effectiveness in reducing diarrhoea mortality rates.

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RÉSUMÉ

INTERVENTIONS POUR LA LUTTE CONTRE LES MALADIES DIARRHÉIQUES CHEZ LES JEUNES ENFANTS : PROGRAMMES D'ALIMENTATION COMPLÉMENTAIRE

Ce document est le deuxième d'une série d'études sur les interventions possibles en vue de réduire la morbidité et la mortalité par maladies diarrhéiques parmi les enfants de moins de 5 ans dans les pays en développement. On admet depuis de nombreuses années qu'il existe une synergie entre les maladies diarrhéiques et l'état nutritionnel, et d'importantes recherches ont été effectuées en vue d'élucider la nature de cette synergie. D'après certains experts, l'amélioration de l'état nutritionnel grâce à des programmes d'alimentation complémentaire pourrait constituer une stratégie efficace pour réduire les taux de maladies diarrhéiques chez les enfants d'âge préscolaire. Par programme d'alimentation complémentaire, on entend ici la distribution planifiée de denrées destinées à améliorer l'apport alimentaire chez les enfants d'âge préscolaire (la fourchette d'âge habituelle des enfants cibles est de 6 mois à 5–6 ans). Les aliments distribués peuvent être soit «à emporter à domicile», soit destinés à être consommés sous surveillance dans des centres d'alimentation. Ces programmes d'alimentation complémentaire peuvent viser la totalité d'un groupe d'âge et de sexe définis ou bien des enfants atteints de degrés particuliers de carence nutritionnelle.

Les preuves qu'un état nutritionnel médiocre prédispose à une incidence accrue de maladies diarrhéiques ou que des programmes d'alimentation complémentaire peuvent réduire cette incidence sont assez fragiles. Toutefois, des observations ont montré qu'un état nutritionnel médiocre prédispose à des diarrhées plus graves et à une létalité plus élevée, et que les programmes d'alimentation complémentaire sont capables de réduire la gravité des diarrhées et la mortalité qu'elles causent. Ces programmes entraînent des dépenses élevées et sont très complexes au point de vue de la logistique et de la gestion; en outre, ils n'ont pas réussi à améliorer de manière notable l'état nutritionnel d'enfants âgés de 6 á 23 mois, c'est à dire de ceux justement parmi lesquels les taux de morbidité et de mortalité par diarrhées sont le plus élevés. Il est peu probable que les programmes d'alimentation complémentaire soient une intervention d'un bon rapport coût/rendement pour les programmes nationaux de lutte contre les maladies diarrhéiques.

L'alimentation thérapeutique n'a pas été incluse dans cette étude. Une telle alimentation peut sauver la vie d'un enfant atteint de malnutrition sévère. Ne sont pas non plus considérés les programmes d'alimentation mis en œuvre dans les situations d'urgence ou de catastrophe, dans lesquelles la pénurie d'aliments peut être une cause de malnutrition pour la majorité des enfants. Sont étudiés ici les programmes d'alimentation complémentaire visant à accroître l'apport alimentaire des enfants d'âge préscolaire sur plusieurs années et sur la base d'une collectivité tout entière. De tels programmes sont coûteux, incapables de réduire les taux de morbidité par diarrhée, et leur efficacité est douteuse en ce qui concerne la réduction des taux de mortalité par diarrhée.

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Annex 1

SUMMARY OF SUPPLEMENTARY FEEDING PROGRAMMES THAT WERE EVALUATED FOR IMPACT ON MORBIDITY OR MORTALITY

Country	Rural/ urban	Dates of feeding programme	Target children	Feeding programme	Participation	Educational programme for mothers	Other intervention
Colombia	urban	1964–65	Malnourished children, 0–71 mo; plus their siblings and pregnant or lactating mothers	Weekly collection of take-home allocation of 1 pound of dried skimmed milk per child per week	56% of children enrolled failed to participate regularly throughout 1 year of programme and were excluded from impact analysis	Yes	No
Ethiopia	rural	1965–67	All children 0–11 years	Weekly collection of take-home allocation to provide 335 kcal and 14 g of protein per child per day	Only children receiving > 50% of weekly distributions were included in study	Yes	DPT, TB, and and smallpox vaccination; general curative care provided
Guatemala	rural	1959–64	All children 0–59 mo.	Daily supervised feeding providing 350 kcal and 15 g of protein per child	52% of children of 6–59 mo. participated > 50% of time. Participation of < 6 mo. children was not expected. Participation declined during 5 yrs of programme	Yes	No
Guatemala	rural	1969–76	All children 0–83 mo.	Twice daily supervised feeding at feeding centres	No data	No	Curative and preventive health services, supplementary feeding for pregnant or lactating women

Control community	Changes in nutritional status	Changes in mortality[a]	Causes of death	Morbidity survey, methods	Changes in diarrhoeal disease rates	Cost[b]	Source
No	Malnutrition, judged by weight-for-age decreased substantially during the 1 yr feeding programme	No data	No data	Yes, 1-week recall at visits to nutrition centre	Data on diarrhoea incidence cannot be interpreted owing to lack of controls	No data	*41*
No	Clinical signs of PCM decreased and upper arm circumference-for-age increased. Weight-for-age and height-for-age did not change	No data	No data	Yes, 3-monthly or 6-monthly examinations and stool microscopy	Data on diarrhoea, *Entamoeba histolytica*, *Ascaris*, and hookworms cannot be interpreted owing to lack of controls	No data	*21*
Yes	Proportion of 0–59 mo. children < 90% weight-for-age declined from 91% in 1959 to 83% in 1964. A child in the feeding village could expect to be 30 mm taller and 1 kg heavier at age 5 yrs than a control child	9 yrs prior to intervention compared with 5 yrs of intervention. Crude mortality declined from 25 to 16 per 1000 (36% reduction) 0–11 mo. mortality declined from 182 to 146 per 1000 (19% reduction), 12–59 mo. mortality declined from 56 to 24 per 1000 (56% reduction)	During 5 yrs of programme, the proportion of deaths due to diarrhoea was around 20%	Yes, 2-week recall at home visits	Incidence of diarrhoea cases, among 0–59 mo. children, per year rose from 48 per 1000 in 1959 (control village = 123) to 219 per 1000 in 1964 (control village = 165). This was attributable to falling participation in the feeding programmes. Diarrhoea case-fatality ratios during 1959–64 were 0.8% in the feeding village and 1.7% in the control village. The proportions of cases judged to be severe (blood or mucous or duration > 3 days) were 10% in the feeding village and 20% in the control village	No data	*5, 18, 19, 33, 34*
Internal controls	Children of 9–59 mo. who regularly took supplement had weight and height gains 10–15% higher than other children	Using before-and-after comparisons, 0–11 mo. mortality declined from 150 to 55 per 1000 (63% reduction) and 12–59 mo. mortality declined from 28 to 6 per 1000 (79% reduction). 70% of these reductions were attributed to health care and 30% to nutrition, especially nutrition of pregnant mothers	No data	No	No data	US$ 7.2 per capita per year for health services. Nutrition component costs not available	*20*

[a] All mortality rates for 0–11 mo. children are per 1000 live births. Other mortality rates are per 1000 children in the stated age range.

[b] All costs are given in 1982 US$. Costs in other currencies and years have been converted to 1982 US$ using exchange rates and GNP deflators computed from data in *International financial statistics*.

Country	Rural/ urban	Dates of feeding programme	Target children	Feeding programme	Participation	Educational programme for mothers	Other intervention
India (Punjab)	rural	1970–73	All children 0–35 mo. and < 70% weight for age	Twice daily supervized feeding to provide up to 400 kcal and 11 g of protein per child per day	Attendance by target children averaged 22% for those aged 0–12 mo. and 41% for those aged 13–36 mo.	Yes	Prenatal care, supplementary feeding of underweight mothers
India (Madhya Pradesh): exploratory phase	rural	1971–72	All children 6–35 mo.	Weekly collection of take-home allocation to provide 377 kcal and 19 g of protein per child per day	53% of available food was collected	Yes	Preventive and curative health care. Supplementary feeding for pregnant and lactating mothers
intensive phase	rural	1972–74	as above	as above	< 50% of available food collected	No	No
India (Maharashtra)	rural	1971–79	"Deserving" children 0–59 mo	Daily supervised feeding	No data	Yes	Curative and preventive health services, supplementary feeding for pregnant women
Papua New Guinea	rural	1961–62	All children 6–11 mo.	Weekly collection of take-home allocation to provide 100–280 kcal and 10 g of protein per child per day	35% of children enrolled missed > 15 weeks and were excluded from impact analysis	No	No
Peru	rural	1962–67	All children and all adults	Weekly collection of take-home allocation to provide 250 kcal and 12.5 g of protein per day to all family members	95% of families collected their supplement every week	No	No

Control community	Changes in nutritional status	Changes in mortality[a]	Causes of death	Morbidity survey, methods	Changes in diarrhoeal disease rates	Cost[b]	Source
Yes	Target children > 17 mo. were significantly heavier, and target children >21 mo. were significantly taller, than controls	0–11 mo. mortality was 89 per 1000 compared with 129 per 1000 in control villages. 12–35 mo. mortality was 10 per 1000 compared with 19 per 1000 in control villages	44% of deaths due to diarrhoea in 1970	Yes, 1-week recall at home visits	No effect on diarrhoea incidence or duration demonstrated	US$ 47 per 0–35 mo. child per year for nutrition intervention	*24, 25, 27, 31, 37*
Yes	Significant improvement in weight-for-age for regular (> 50% of collections) collectors of food	No data	No data	Yes, 2-month recall at start and end of intervention	Significant reduction in diarrhoea incidence among 24–35 mo. age group, but not among younger children	US$ 57 per child per year for the complete intervention package	*17*
Yes	Significant improvement in weight-for-age but not as great as achieved by complete package (see above)	No significant reduction	4.5% of deaths among 0–47 mo. children attributed to diarrhoea	No	No data	US$ 39 per child per year for the nutrition intervention alone	
Yes	No data	In 1976, 0–11 mo. mortality was 39 per 1000 in project area and 90 per 1000 in control area	No data	No	No data	US$ 2.5 per capita per year for complete intervention package	*2, 3, 4*
Yes	Supplementary feeding did not affect height or weight gain	No data	No data	Yes, monthly examination and stool microscopy	Supplementary feeding did not influence the value of a composite "illness score" that included diarrhoea and dysentery	No data	*9*
Yes	No clear evidence that the supplementary feeding improved the nutritional status or growth of any age group. This poor response was attributed to the supplementary foods displacing traditional foods	0–11 mo. mortality was significantly lower in intervention villages (44–52 per 1000) than in control villages (104–165 per 1000). 12–59 mo. mortality was not significantly reduced	No data	No	No data	No data	*6*

[a] All mortality rates for 0–11 mo. children are per 1000 live births. Other mortality rates are per 1000 children in the stated age range.

[b] All costs are given in 1982 US$. Costs in other currencies and years have been converted to 1982 US$ using exchange rates and GNP deflators computed from data in *International financial statistics*.

CH 3.2

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Interventions for the control of diarrhoeal diseases among young children: measles immunization*

R. G. FEACHEM[1] & M. A. KOBLINSKY[2]

The effects of measles immunization on diarrhoea morbidity and mortality are reviewed using data from field studies and theoretical calculations. Two types of measles-associated diarrhoea are distinguished: with-measles diarrhoea, which starts between 1 week pre-rash-onset and 4 weeks post-rash-onset, and post-measles diarrhoea, which starts 4–26 weeks post-rash-onset. The etiology of these measles-associated diarrhoeas is unknown, but some evidence points towards a frequently severe and dysenteric form of disease, with Shigella *playing a major role. Theoretical calculations indicate that measles immunization, at the age of 9–11 months, with coverage of between 45% and 90% can avert 44–64% of measles cases, 0.6–3.8% of diarrhoea episodes, and 6–26% of diarrhoea deaths among children under 5 years of age. The cost of measles immunization is in the range of US$ 2–15 (1982 prices) per child vaccinated. The impact of measles immunization on diarrhoea mortality may be partly additional to the impact of oral rehydration because it averts deaths that are not prevented by oral rehydration. Community research is urgently needed to confirm or reject these theoretical suppositions, to clarify the etiology of measles-associated diarrhoea, and to determine the cost-effectiveness of measles immunization as an intervention to reduce diarrhoea mortality.*

Measles immunization is now an integral part of the Expanded Programme on Immunization (EPI) which many developing countries are implementing with the support of the World Health Organization. In some developed countries, e.g., Czechoslovakia and the USA, the elimination of measles may soon be achieved (*12*). There is a marked association between measles and diarrhoea in developing countries today, as there was in developed countries in earlier times (*20*). Since cases of measles complicated by diarrhoea have a high fatality rate, measles immunization is a potential intervention for diarrhoea control. This review of the role of measles immunization in diarrhoeal disease control is the first in a series of reviews of potential anti-diarrhoea interventions which will be published in the *Bulletin of the World Health Organization* (*9*).

EFFECTIVENESS

For measles immunization to be an effective diarrhoea control intervention, the following hypotheses have to be tested and proved:

either

a considerable proportion of diarrhoea morbidity or mortality in young children in developing countries is associated with measles	*hypothesis 1*

and

measles immunization can reduce the incidence of measles	*hypothesis 2*

or

measles immunization can reduce diarrhoea morbidity or mortality rates in young children	*hypothesis 3*

* Requests for reprints should be sent to the Programme Manager, Diarrhoeal Diseases Control Programme, World Health Organization, 1211 Geneva 27, Switzerland.

[1] Reader in Tropical Public Health Engineering, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, England.

[2] WHO Consultant.

If hypotheses 1 and 2 are true, it could be appropriate to field test hypothesis 3; whereas if hypothesis 3 is known to be true, measles immunization could be recommended as an operational component of national diarrhoeal diseases control programmes. The evidence for and against these hypotheses is examined below.

Hypothesis 1. *A considerable proportion of diarrhoea morbidity or mortality in young children in developing countries is associated with measles*

Definitions

Two kinds of measles-associated diarrhoea are distinguished in this review; with-measles diarrhoea and post-measles diarrhoea. With-measles diarrhoea is diarrhoea occurring in close association with an attack of measles and is defined, arbitrarily, by the period of time separating the appearance of the measles rash and the onset of diarrhoea. Authors differ in their definition of this time period. Scrimshaw et al. (*25*) reported diarrhoea episodes in 127 measles-infected Guatemalan children, under 5 years of age, which occurred from 2 weeks pre-rash-onset to 2 weeks post-rash-onset and found that the great majority of diarrhoea episodes started between 8 days pre-rash-onset and 5 days post-rash-onset. These authors subsequently defined the time limits of with-measles diarrhoea as that starting between 7 days pre-rash-onset and 7 days post-rash-onset. In a study in Nigeria of 142 children suffering from measles and diarrhoea (*20*), it was found that the diarrhoea started 14–7 days pre-rash-onset in 5% of cases, 6–1 days pre-rash-onset in 19% of cases, 0–6 days post-rash-onset in 25% of cases, 7–14 days post-rash-onset in 11% of cases, and more than 14 days post-rash-onset in 40% of cases. This high (40%) proportion of diarrhoea occurring more than 2 weeks after the rash-onset may be related to the phenomenon of post-measles diarrhoea discussed below. Koster et al. (*14*), after studying 119 village children in Bangladesh who had measles and diarrhoea over a 6-month period, reported a marked increase in diarrhoea starting between 1 week pre-rash-onset and 4 weeks post-rash-onset. With-measles diarrhoea is defined, in the present review, as that starting between 1 week pre-rash-onset and 4 weeks post-rash-onset, although it must be cautioned that most studies do not report the exact time frame but imply that with-measles diarrhoea occurs shortly before or during the exanthem.

A second type of measles-associated diarrhoea, called here post-measles diarrhoea, was hinted at by some earlier writers and has recently been investigated in Bangladesh. Morley et al. (*20*), for example, reported from Nigeria that children "were susceptible to diarrhoea for a long period after the measles itself had subsided" and that "the diarrhoea may continue or reappear over a period of many weeks". More recently, in Bangladesh, a substantial predisposition to dysentery, though not to watery diarrhoea, was found in children for a period of five months following an attack of measles.[a] There is thus some evidence for a phenomenon of post-measles diarrhoea, which is defined here, arbitrarily, as diarrhoea occurring in the period 4–26 weeks post-rash-onset, over and above that which could occur in that age group at any time.

In summary, the total of measles-associated diarrhoea cases is defined here as the sum of with-measles diarrhoea cases (starting between 1 week pre-rash-onset and 4 weeks post-rash-onset) and post-measles diarrhoea cases (starting 4–26 weeks post-rash-onset). There is, as yet, very little information on the magnitude or nature of post-measles diarrhoea.

Measles-associated diarrhoea morbidity

The proportion of diarrhoea episodes that are measles-associated can be derived theoretically and from the results of field studies.

Among children aged 0–59 months in developing countries, there are on average 2.2 episodes of diarrhoea per year per child (*26*). If we assume that every child also has measles before 5 years of age and that every measles case has one associated diarrhoea episode, then in the first five years of life an average child will have 11 episodes of diarrhoea, of which 1 is measles-associated diarrhoea. Therefore a theoretical upper proportion of measles-associated diarrhoea to all diarrhoea in the first five years of life is 9%.[b] A review of 10 community-based studies in 5 countries[c] shows that only 15–63% of measles cases in children have accompanying diarrhoea. Using these extreme figures, the proportion of diarrhoea in the first 5 years of life that is with-measles diarrhoea is 1.0–4.0%, assuming that 70% of children have measles before they are 60 months old (70% is the median figure from 18 studies in 10 countries[c]). In addition, data on post-measles diarrhoea from Bangladesh suggest that 18% of children who have measles will experience an episode of diarrhoea in the following 6 months, which they would not otherwise have had.[d] By the addition of these post-measles diarrhoea episodes, it is calculated that 2.1–5.2% of diarrhoeal episodes in the first 5 years of life are measles-associated, assuming that 70% of children contract measles before the age of 60

[a] SHAHID, N. S. ET AL. *Long-term complication in measles in rural Bangladesh.* International Centre for Diarrhoeal Disease Research, Bangladesh, 1982 (unpublished report).

[b] This is not the theoretical maximum proportion since it is possible that each measles attack is associated with more than 1 diarrhoea episode.

[c] Tabulated data and sources are available on request from R.G.F.

[d] See footnote *a*, above.

demics occur in the cool, dry season when diarrhoea incidence is at its lowest.

In summary, theoretical considerations indicate that 1–7% of diarrhoea episodes in under-5-year-old children may be measles-associated (Table 1), while studies in Nigeria and Guatemala both report a figure of 6%.

Measles-associated diarrhoea mortality

As with measles-associated diarrhoea morbidity, the proportion of diarrhoea deaths that are measles-associated may be derived theoretically and from field data.

Theoretically computed measles-associated diarrhoea incidence rates are presented in Table 1. They range from 3 to 14 cases per year per 100 children aged 0–59 months. By the application of case-fatality rates to these incidences, mortality rates for measles-associated diarrhoea may be derived. The case-fatality rates for measles-associated diarrhoea are high. A review of 13 studies from 11 countries[c] shows that in hospitals, which tend to see more severe cases, 5–29% of young children with measles and diarrhoea die, whereas fatality rates reported from community studies are between 2% and 9%. In Table 2, three possible case-fatality rates (3%, 6% and 9%) are applied to three possible measles-associated diarrhoea incidence rates (4, 8 and 12 per 100 children aged 0–59 months) to obtain a range of measles-associated diarrhoea mortality rates. These mortality rates are then compared with an overall diarrhoea mortality rate of 1.4 per 100 under-5-year-old children per year (*26*) to obtain the proportions of diarrhoea deaths that are measles-associated. The range of proportions is considerable (9–77%), and is subject to the important cautions given in the footnote to Table 2.

Only one field report giving the proportion of diarrhoea deaths that are measles-associated has been located (*14*). It describes a one-year surveillance of 5775 rural Bangladeshi children under 10 years old, 29 of whom died of diarrhoea alone and 15 of diarrhoea with measles (death within one month of rash-onset). Thus, 34% of these diarrhoea deaths were measles-associated. In this same study, a further 8 children died with measles complicated by a combination of diarrhoea and respiratory symptoms or by various other complications. If 2 of these 8 deaths are included as deaths from measles-associated diarrhoea, the proportion of diarrhoea deaths that were measles-associated rises from 34% to 37%. These data relate to 0–9-year-old children, not 0–4 years as in Table 2. The effect of considering this older age group may be to increase the proportion of diarrhoea deaths that are measles-associated because the mortality rate from all diarrhoeas declines more rapidly after 5 years of age than does the mortality rate for measles. Expressing the mortality rate among 6–9-year olds as a percentage of the rate among 4–5-year olds, the same researchers (*14*) found that it was 6% for diarrhoea and 23% for measles. This effect may be partly counteracted by the exclusion from these data of deaths due to post-measles diarrhoea.

In summary, theoretical considerations indicate that perhaps 9–77% of diarrhoea deaths in the first 5 years of life are measles-associated, while the one field study providing data on this suggests a figure of 37% (for 0–9-year-old children).

Etiology of measles-associated diarrhoea

The etiology of measles-associated diarrhoea remains largely unknown. The high case-fatality rates, however, suggest a severe form of the disease.

Table 2. The proportion of diarrhoea deaths in the first five years of life that is measles-associated, based on various assumptions

Measles-associated diarrhoea incidence per 100 children aged 0–59 months per year	Case-fatality rate for measles-associated diarrhoea (%)	Measles-associated diarrhoea mortality per 100 children aged 0–59 months per year	Proportion of all diarrhoea deaths among children aged 0–59 months that are measles-associated (%)[a]
4	3	0.12	8.6
4	6	0.24	17.1
4	9	0.36	25.7
8	3	0.24	17.1
8	6	0.48	34.3
8	9	0.72	51.4
12	3	0.36	25.7
12	6	0.72	51.4
12	9	1.08	77.1

[a] These calculations assume that the annual mortality rate from diarrhoea in the first five years of life is 1.4 per 100 children (*26*). In areas where children die more frequently from diarrhoea than this, the proportion of deaths that are measles-associated will be lower, while in areas where the diarrhoea death rate is lower, the proportion will be higher. It is further assumed that measles-associated diarrhoea deaths are recorded as diarrhoea deaths. In the case of post-measles diarrhoea deaths this is a reasonable assumption, but many with-measles diarrhoea deaths will be recorded as deaths from measles rather than deaths from diarrhoea. If all with-measles diarrhoea deaths were recorded as measles deaths, the proportions given in the final column should be reduced by 50–86% (see Table 1). These calculations also assume that the case fatality rates for with-measles diarrhoea and post-measles diarrhoea are the same; there is no evidence on which to judge the correctness of this assumption.

[c] Tabulated data and sources are available on request from R.G.F.

months. This calculation is sensitive to the assumptions made about the proportion of measles cases that have with-measles or post-measles diarrhoea and to the assumption that 70% of children have measles before they are 60 months old. Table 1 presents the proportions of diarrhoeas in the first 5 years of life that may be measles-associated, based on different values of these parameters. The range of proportions is 1.4–6.6%, and is subject to the cautions given in the footnote to Table 1.

Data from community studies support this theoretical range. In Imesi, Nigeria, 259 children under 5 years old averaged 2.3 episodes of diarrhoea per year per child over a 3-year period, of which 0.14 (or 6%) were measles-associated (*20*). In Santa Cruz Balanya, Guatemala, each child under 5 years of age was found to suffer an average of 1.65 episodes of diarrhoea in the year commencing April 1963 (*10*). During a 4-month period of that year, there was a measles epidemic in the village and, during that time, a child suffered on average 0.6 episodes of diarrhoea of which 0.098 were with-measles diarrhoea. Therefore, computed over the year and assuming that no measles occurred outside the period of the epidemic, the proportion of diarrhoea episodes that were measles-associated was 6%. The proportion over the period of the epidemic only was 16%, thus illustrating the manner in which measles-associated diarrhoea becomes more prominent during a measles epidemic and especially when, as commonly occurs, measles epi-

Table 1. The proportion of diarrhoea episodes in the first five years of life that is measles-associated, based on various assumptions

Proportion of measles cases having with-measles diarrhoea (%)	Proportion of measles cases having post-measles diarrhoea (that they would not otherwise have had) (%)	Proportion of children contracting measles before age 60 months (%)	Measles-associated diarrhoea incidence per 100 children aged 0–59 months per year	Proportion of all diarrhoea episodes among children aged 0–59 months that is measles-associated (%)[a]
20	10	90	5.4	2.6
20	10	70	4.2	1.9
20	10	50	3.0	1.4
20	20	90	7.2	3.3
20	20	70	5.6	2.6
20	20	50	4.0	1.8
40	10	90	9.0	4.1
40	10	70	7.0	3.2
40	10	50	5.0	2.3
40	20	90	10.8	4.9
40	20	70	8.4	3.8
40	20	50	6.0	2.7
60	10	90	12.6	5.7
60	10	70	9.8	4.5
60	10	50	7.0	3.2
60	20	90	14.4	6.6
60	20	70	11.2	5.1
60	20	50	8.0	3.6

[a] These calculations assume that, on average, a child has 2.2 episodes of diarrhoea per year in the first five years of life (*26*). In areas where children have more frequent diarrhoea, the proportion that is measles-associated will be lower, while where diarrhoea is less frequent, the proportion that is measles-associated will be higher. It is further assumed that measles-associated diarrhoea is recorded as diarrhoea in surveillance data and thus forms a part of the 2.2 episodes of diarrhoea per child per year. In the case of post-measles diarrhoea this is almost certainly a correct assumption, but with-measles diarrhoea may be recorded as a complication of measles rather than a case of diarrhoea.

Table 3. Reported coverage rates for measles immunization in some developing countries reporting > 50% coverage as at 1982

WHO Region	Country or area	Reported coverage (%)*
Africa	Botswana	63
	Gambia	61
	United Republic of Tanzania	82
Americas	Argentina	60
	Brazil	58
	Chile	88
	Costa Rica	68
	Ecuador	67
South-East Asia	Maldives	98
	Mongolia	98
Europe	Turkey	52
Eastern Mediterranean	Bahrain	63
	Egypt	63
	Islamic Republic of Iran	81
	Israel	69
	Kuwait	71
	Libyan Arab Jamahiriya	65
	Tunisia	65
Western Pacific	American Samoa	86
	Brunei	73*
	Hong Kong	74*
	Niue	77*
	Singapore	86
	Trust Territory of the Pacific Islands	53*

* Coverage rates refer to the proportion of children vaccinated by 12 months, except in cases marked * where they describe immunization coverage by 60 months. For most countries the figures refer not to the whole country but to selected regions where measles immunization has been initiated on a pilot basis.

(Source: Data reported to WHO)

figure of 75%, bearing in mind that the relevant coverage figure is not what is now being achieved in countries with only limited immunization programmes, but what might be reasonably expected in countries committed to measles immunization and with a national programme built up over several years.

Thus, of the 756 children requiring measles vaccine, 567 (75%) will be vaccinated. The remaining 189 will not be vaccinated and an estimated 66%,[†] or 125 of these, will go on to contract measles before month 60.

Of the 567 vaccinated children, a proportion would have been immunized successfully. The not successfully immunized ones will be those who were susceptible but failed to seroconvert, plus those who were not susceptible because of persisting maternal antibodies. The seroconversion rate at 9–11 months, based on reports from developing countries, is generally > 90% although lower figures have also been reported (Table 4). High seroconversion rates are reported from carefully organized research studies in which the vaccine's potency is well maintained. Seroconversion rates in on-going immunization programmes are probably lower because of operational factors. In addition, a small proportion of children (probably 1–5%) at ages 9–11 months are not susceptible owing to persisting maternal antibodies. Taking these considerations into account, it may be assumed for the present example that 90% of children without a history of measles who are vaccinated at ages 9–11 months will seroconvert and be immune to measles. In Table 5, two seroconversion rates have been adopted for comparison (80% and 90%). Thus, of the 567 vaccinated children, 510 (90%) would have been effectively immunized and 57 would not; 38 (66%) of these 57 would then go on to contract measles before month 60.[†]

In summary, out of 1000 children born alive, the following will get measles between months 0 and 60: 3 will have measles and then die before 9–11 months, 94 will have measles and recover before 9–11 months, 125 will not be vaccinated and will go on to get measles before month 60, and 38 will be vaccinated but will nevertheless get measles before month 60. This makes a total of 260 measles cases.

The number of measles cases in the absence of an immunization programme may be computed in a similar manner. Of 1000 children born alive, 150 will die before 12 months and 3 of these will have measles before they die. Of the remaining 850, approximately 70% (or 595) will have measles before the age of 60 months. This makes a total of 598 measles cases in the first five years of life. Therefore, in the first five years of life, the number of measles cases averted per 1000 live births by a measles immunization programme will be 338 (598–260), or 57%.

This calculation is presented in Table 5, using four levels of programme coverage (45%, 60%, 75% and 90%), and two rates of successful seroconversion after measles immunization at 9–11 months of age (80% and 90%). A correction using infant mortality

[†] If 11% have measles before 12 months, and 70% before 60 months, the proportion of those who have not had measles at 12 months but who will have it by 60 months is 66%.

Indications that with-measles diarrhoea may be primarily dysenteric in nature are based on reports from several studies. Thus, blood was commonly present in the stools of Gambian village children suffering from with-measles diarrhoea (*16*). Hospital data from East and West African countries found 62% (*21*) and 65% (*22*), respectively, of with-measles diarrhoea to be mucoid or mucoid and bloody, or to be associated with anal prolapse. In the above reports, bloody and mucoid diarrhoeas with measles were more fatal than those described as mucoid only (11% vs 6% in East Africa; 18% vs 11% in West Africa), although the mucoid diarrhoeas were the majority of the dysenteric diarrhoeas (68% and 72% respectively). Bacteriological examination detected *Shigella* species in "approximately 50%" of faecal samples from children having with-measles diarrhoea in Bangladesh (*14*). Although this observation was uncontrolled, it may be contrasted with the typical 4–10% isolation rates of *Shigella* from paediatric diarrhoea cases in the same area of Bangladesh (*2*). In Bangladesh it was also observed (*14*) that the with-measles diarrhoea cases were of significantly longer average duration (51% of episodes lasting more than 6 days) than other diarrhoeas (only 25% of episodes lasting more than 6 days). Immunological factors that may account for the association between measles and diarrhoea have been reviewed by Greenwood & Whittle (*11*).

With regard to post-measles diarrhoea, recent evidence from Bangladesh suggests the predominance of dysentery.[f] In a comparison of children in the five months after measles with matched controls, it was found that the attack rates for watery diarrhoeas were 47% in the post-measles cases and 56% in the controls (not significant), whereas the attack rates for mucoid diarrhoeas were 42% among the cases and 19% among the controls ($P < 0.01$) and the attack rates for bloody diarrhoeas were 21% among cases and 9% among controls ($P < 0.05$).

In contrast to these findings, a hospital study in Kenya (*23*) reported that, of 200 rectal swabs taken from children having with-measles diarrhoea, only 3 were positive for *Shigella* and 1 for *Salmonella*; the stools of these patients were described as bloody and mucoid. The case-fatality rate in this Kenyan series was, however, high at 29%. A study of 54 children hospitalized with measles and diarrhoea in Rwanda found *Shigella* in the stool of only 1 child, whereas *Salmonella* was found in 16 (*7*). A retrospective study in Thailand found diarrhoea to be a common complication of hospitalized measles (26%), but the diarrhoea was reported to be rarely severe and almost always responded to oral rehydration.[g] Interestingly, measles in general was not considered to be especially life-threatening in Thailand, and the hospital case-fatality rate for all measles cases was only 2.3%.

The etiology of measles-associated diarrhoea, and in particular the role of *Shigella* and other agents of dysentery, requires urgent investigation. Such studies are under way, with WHO support, in Rwanda and should be conducted in other sociocultural and environmental settings as well.

Hypothesis 2. *Measles immunization can reduce the incidence of measles*

The experience of some developed countries, such as Czechoslovakia and the USA which are close to measles elimination, clearly shows that measles immunization can reduce the incidence of measles very greatly (*12*). In developing countries, however, many factors intervene to reduce the overall impact of a measles immunization programme.

Consider, for example, a group of 1000 children born alive. By the age of immunization (usually 9–11 months), 150 will have died,[h] and a proportion of those surviving will have had measles. Data from 18 studies in 10 developing countries show that the proportion of children contracting measles before the age of immunization is 4–25% and that the figure is generally higher in urban than in rural areas;[i] the figure of 11% will be adopted here as it is the median figure from the data reviewed. Therefore, of the 850 children surviving to immunization age, 11% or 94 would have had measles and it will be assumed that a further 2%, or 3 of the 150 children who died earlier, had measles before they died. Therefore, out of the 1000 children born in month 0, there will be 97 measles cases by month 12.

During months 9–11, the 850 surviving children will be the subjects of a measles immunization programme; 756 (850 – 94) would not have had measles and a proportion of these will receive the vaccine. This proportion depends on the programme coverage. Theoretically, this coverage can be 100% but in practice it is lower. As many countries do not have an effective measles immunization programme, the coverage figures for a whole region are generally less than 10%. The coverage figures for individual selected countries can be higher (Table 3), although some of the figures reported are very optimistic estimates. In subsequent tabulations (Tables 5 and 6), four possible coverage figures have been adopted for comparative purposes (45%, 60%, 75% and 90%). For the present example, we shall assume a coverage

[f] See footnote *a*, page 642.

[g] WARD, N. A. *Survey to determine mortality and morbidity patterns in measles, Thailand.* Unpublished WHO document SEA/EPI/5, 1979.

[h] The infant mortality rate varies greatly among countries. A figure of 150 is adopted for the purposes of this illustrative example. No allowance is made for mortality after 1 year of age.

[i] Tabulated data and sources are available on request from R.G.F.

portion of measles cases averted in under 5-year-old children, as a result of the measles immunization programme.

Hypothesis 3. *Measles immunization can reduce diarrhoea morbidity or mortality rates in young children*

Field reports on the effect of measles immunization on diarrhoeal disease rates have been looked for without success, although studies of this type are under way in Bangladesh and possibly elsewhere.

The only approach, at present, to assessing hypothesis 3 is, therefore, a theoretical one using information computed during the assessment of hypotheses 1 and 2. If, among under-5-year-old children, 4% of diarrhoea morbidity (Table 1) and 30% of diarrhoea mortality (Table 2) were measles-associated, and if 54% of the measles cases could be averted by measles immunization with a coverage of 75% (Table 5), then measles immunization might reduce diarrhoea morbidity by 2.2% and diarrhoea mortality by 16% in children in this age group. Table 6 presents the results of these computations for various values of measles-associated diarrhoea morbidity (2%, 4% and 6%), measles-associated diarrhoea mortality (20%, 30% and 40%), and immunization programme coverage (45%, 60%, 75% and 90%). It is concluded that measles immunization among children aged 0–59 months may reduce diarrhoea morbidity by 0.6–3.8% and diarrhoea mortality by 6–26%. These calculations all depend on the assumption that, if a case of measles is averted by immunization, the diarrhoea (both with-measles and post-measles) associated with that case of measles will also be averted. This is only true if measles-associated diarrhoea is actually "caused" by measles (not necessarily in the sense that the measles virus causes the diarrhoea but in the more general sense that measles infection leads to diarrhoea by still unknown immunological or pathological mechanisms) and not because the susceptibilities to measles and diarrhoea are both dependent on some other factor.

The proportions of diarrhoea morbidity and mortality averted in children under 5 years of age are likely to increase as the immunization programme continues and herd immunity rises, with a consequent decrease in the proportion of children acquiring measles before the age of immunization and an in-

Table 6. Reduction of diarrhoea morbidity and mortality in the first five years of life by measles immunization at various levels of coverage

Coverage of measles immunization (%)	Proportion of measles cases averted by measles immunization (see Table 5) (%)	Proportion of diarrhoea episodes that are measles-associated (see Table 1) (%)	Proportion of of diarrhoea episodes averted by measles immunization[a] (%)	Proportion of diarrhoea deaths that are measles-associated (see Table 2) (%)	Proportion of diarrhoea deaths averted by measles immunization[a] (%)
45	32	2	0.6	20	6.4
45	32	4	1.3	30	9.6
45	32	6	1.9	40	12.8
60	44	2	0.9	20	8.8
60	44	4	1.8	30	13.2
60	44	6	2.6	40	17.6
75	54	2	1.1	20	10.8
75	54	4	2.2	30	16.2
75	54	6	3.2	40	21.6
90	64	2	1.3	20	12.8
90	64	4	2.6	30	19.2
90	64	6	3.8	40	25.6

[a] These calculations assume that measles-associated diarrhoea occurs with equal frequency among measles cases that are and are not averted by measles immunization. If failure to be immunized and measles-associated diarrhoea are both associated with an independent factor (say, low socioeconomic status), then this assumption does not hold and the impact on diarrhoea of measles immunization will be lower than predicted here.

Table 4. Age-specific seroconversion rates following measles immunization

Country	Seroconversion rate (%) at:							Reference
	6	7	8	9 months	10	11	12	
Africa								
Kenya	52	72	86	95	98			*29*
Nigeria							94[a]	*13*
South Africa	23	45	57	86	71	86	80	*8*
United Republic of Tanzania		44		63		74		*28*
Upper Volta	76	90	97					*17*
Zimbabwe	59			97				*4*
North America								
USA							80–85	*15*
South America								
Chile	57	59		99				*3*
3 countries:[b]								*5*
well nourished[c]	59	69	84	87	93	94	97	
undernourished[d]	81	91	93	94	90	96	86	

[a] Children aged 12–23 months
[b] Brazil, Chile and Ecuador
[c] > 85% weight-for-age
[d] 60–85% weight-for-age

rates is not shown in Table 5 because these rates affect equally the communities both with and without a measles immunization programme and they do not change the computed proportions of measles cases averted. The proportion of measles cases in children aged 0–59 months averted by measles immunization (Table 5) is between 30% and 68%, depending on the programme coverage and, to a lesser extent, on the assumed seroconversion rate. The reader who is interested in a particular locality and knows that the programme coverage, seroconversion rate and age at immunization are different from those assumed above may use his figures and make a calculation to obtain the percentage of measles cases averted.

These calculations reflect the situation of a community having no measles immunization and the same community immediately after the implementation of a measles immunization programme with a specified level of coverage. As this programme continues, the age distribution of measles cases will shift upwards, reducing the proportion of children who acquire measles before the age for immunization and increasing the proportion of unimmunized children who acquire measles after their fifth birthday. Both these changes will cause an increase in the pro-

Table 5. Proportion of measles cases averted in the first five years of life by measles immunization, based on various assumptions on coverage and the proportion of children successfully immunized[a]

Measles immunization coverage (%)	Proportion of children successfully immunized[b] (%)	Proportion of cases averted among 0–4-year-old children (%)
45	80	30
45	90	34
60	80	41
60	90	46
75	80	51
75	90	57
90	80	61
90	90	68

[a] The logic and assumptions underlying these computations are set out in an illustrative example in the text.
[b] The proportion of children not having had measles who, when vaccinated at 9–11 months of age, are subsequently immune to measles.

most reliable. Unfortunately these costs refer to BCG and DPT (rather than measles) immunization. Measles immunization may be cheaper than BCG plus DPT, since it is a single-dose vaccine. As only 10–20% of the cost of an immunization programme is due to the vaccines (*6*), the additional cost of adding measles immunization to an existing EPI programme may be low. A reason for the apparently high cost figure from Ivory Coast (Table 7) is that the reverse approach was taken, 75% of all shared EPI costs being allocated to measles immunization. This has the effect of making measles immunization appear expensive, while other immunizations appear relatively cheap.

Future research will generate improved data on the cost and impact of measles immunization and will permit cost-effectiveness comparisons of measles immunization with other diarrhoea control interventions. Care is required in the allocation of costs and benefits between diarrhoeal disease control programmes (CDD) and EPI programmes and it must be recognized that many with-measles diarrhoea deaths are recorded as measles deaths (see footnote to Table 2). On the other hand, measles immunization may avert a considerable number of post-measles diarrhoea deaths that are not currently accounted for in evaluations of the impact of measles immunization programmes (*1*).

CONCLUSIONS

A theoretical case has been made out that measles immunization can substantially reduce diarrhoea mortality among children under five years of age. Immunization with a coverage of 60% may reduce diarrhoea mortality in children aged 0–59 months by 9–18%, coverage of 75% may reduce diarrhoea mortality by 11–22%, and coverage of 90% may reduce diarrhoea mortality by 13–26% (see Table 6). The impact of measles immunization on diarrhoea mortality is likely to increase as the measles immunization programme continues and the age distribution of measles cases shifts upwards. The impact of measles immunization on diarrhoea mortality may be partly additional to the impact of oral rehydration because it averts deaths that are not prevented by oral rehydration. Community research is urgently needed to confirm or reject these theoretical suppositions and to clarify the etiology of measles-associated diarrhoea.

If community studies confirm that measles immunization can reduce diarrhoea mortality, over and above the reduction achieved by oral rehydration, detailed cost-effectiveness analyses are required to compare measles immunization with other possible interventions for averting the same diarrhoea deaths.

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RÉSUMÉ

STRATÉGIES POUR LA LUTTE CONTRE LES MALADIES DIARRHÉIQUES CHEZ LES JEUNES ENFANTS: VACCINATION ANTIROUGEOLEUSE

Cette étude est la première d'une série consacrée aux stratégies susceptibles d'abaisser la morbidité et la mortalité dues aux maladies diarrhéiques chez les enfants de moins de cinq ans dans les pays en développement. On constate actuellement dans ces pays, comme jadis dans les pays aujourd'hui développés, une nette association entre la rougeole et la diarrhée; la vaccination antirougeoleuse représente donc une arme possible dans la lutte antidiarrhéique. Sur la base de données provenant d'enquêtes sur le terrain et de calculs théoriques, les auteurs de l'étude passent en revue les effets de la vaccination antirougeoleuse sur la morbidité et la mortalité dues aux maladies diarrhéiques. De 1% à 7% des épisodes diarrhéiques et de 9% à 77% des décès par maladie diarrhéique chez les enfants de moins de cinq ans pourraient être liés à la rougeole. Une distinction est faite entre deux types de maladies diarrhéiques associées à la rougeole: la diarrhée concomitante, dont le début se situe entre la semaine précédant l'apparition de l'éruption et les quatre semaines consécutives à celle-ci, et la diarrhée post-rougeoleuse qui commence de 4 à 26 semaines après l'apparition de l'éruption. L'étiologie de ces diarrhées liées à la rougeole est inconnue, mais certains indices laissent penser qu'il pourrait s'agir d'une forme fréquemment sévère et dysentérique de la maladie, dans laquelle *Shigella* jouerait un rôle primordial. Selon des calculs théoriques, la vaccination antirougeoleuse pratiquée entre 9 et 11 mois, avec une couverture vaccinale comprise entre 45% et 90%, serait à même d'empêcher de 44% à 64% des cas de rougeole, de

crease in the proportion of unimmunized children acquiring measles after their fifth birthday.

As the estimated mortality reduction is considerable, there is a need for field studies to assess the role of measles immunization in reducing diarrhoea mortality. If a considerable proportion of measles-associated diarrhoea is dysenteric in nature, it may respond poorly to oral rehydration therapy in the home or at a peripheral health centre. Thus the mortality averted by measles immunization (6–26%) may be, in part, additional to that averted by oral rehydration. This would make measles immunization an especially attractive intervention, since certain other interventions might only reduce the mortality that is largely averted by oral rehydration.

Possibility that diarrhoea is caused by measles immunization. It is necessary to consider whether the above computations require modification because diarrhoea in some children may be caused by measles immunization. Only one controlled study on post-immunization diarrhoea using the further-attenuated vaccine strains (Schwarz and Moraten) has been located. This study, which was carried out in Israel (*27*) among children aged 9–47 months, showed that the period prevalence of diarrhoea during days 6–14 after immunization was 12–14% among children receiving measles vaccines (Schwartz and Moraten) and 12% among children receiving a placebo (sterile saline). A survey of 10 035 children aged between 10 and 18 months, who had been immunized against measles in England, showed that only one child (with a congenital oesophageal atresia) was admitted to hospital with diarrhoea and vomiting one week after the immunization (*18*). A recent review of experience with 131 million cases of measles immunization in the USA did not mention diarrhoea as an adverse reaction (*19*). This limited evidence suggests that diarrhoea is not an adverse reaction to the measles vaccines in current use.

The effect of undernutrition. The role of poor nutritional status in the synergism between diarrhoea and measles has not so far been mentioned in this review. There is evidence that poor nutritional status predisposes to death from both diarrhoea and measles and so it is likely that the death rate from measles-associated diarrhoea is higher among children who are nutritionally deprived. The calculations in this paper are based on data from Africa, Asia and Latin America and reflect the situation in communities with widely differing levels of undernutrition. The calculations are thus generalized across individual countries and environments. In some communities the key variables may approximate the median figures used in this paper, in which case the impact of measles immunization on diarrhoea may be as calculated here. In other communities the key variables may differ considerably from the values used here, in which case the impact of measles immunization on diarrhoea may be considerably greater or less than our calculations. It is likely that in communities where the prevalence of undernutrition is exceptionally high, the impact of measles immunization on diarrhoea mortality will be greater than estimated in this review.

FEASIBILITY

Measles immunization is well established and highly successful in some developed countries (*12*). Some developing countries have initiated measles immunization programmes that are achieving reasonable coverage in selected regions. The main operational difficulties are maintaining vaccine potency and achieving high coverage of children within the target age range (typically 9–11 months). It is expected that, as experience in measles immunization in developing countries grows, and as its benefits to child health become more widely appreciated, these operational difficulties will be overcome.

COSTS

Few developing countries as yet have national measles immunization programmes and there is little reliable information on the cost of such programmes. Table 7 provides cost data for five countries, of which the comparative costings of the EPI programmes in Indonesia, Philippines and Thailand are probably the

Table 7. Costs of immunization

Country	Immunizations	Cost per child vaccinated[a] (1982 US$)	Reference
Indonesia	DPT, BCG	4	*6*
Ivory Coast	measles	15	*30*
Philippines	DPT, BCG	6	*6*
Thailand	DPT, BCG	14	*6*
Zambia:			*24*
rural	measles	8–14	
urban	measles	2–5	

[a] Costs converted to 1982 US$ using exchange rates and GNP deflators computed from data in *International Financial Statistics*.

0,6% à 3,8% des épisodes diarrhéiques, et de 6% à 26% des décès dus à des maladies diarrhéiques chez les enfants de moins de cinq ans. Une couverture vaccinale de 75% permettrait d'éviter 2% des épisodes diarrhéiques et 16% des décès dus à des maladies diarrhéiques. Il n'existe pas de données fiables sur le coût de la vaccination antirougeoleuse, mais d'après des statistiques émanant de cinq pays il pourrait se situer entre 2 et 15 dollars (prix de 1982) par enfant vacciné.

L'impact de la vaccination antirougeoleuse sur la mortalité d'origine diarrhéique devrait augmenter à mesure que se développera le programme de vaccination et que diminuera la proportion des cas de rougeole concernant des enfants. Cet impact viendrait s'ajouter à celui de la réhydratation par voie orale puisque la vaccination tend à prévenir des décès que n'éviterait pas le traitement. Il est urgent de procéder à des enquêtes et études de population pour confirmer ou infirmer ces suppositions théoriques, clarifier l'étiologie de la diarrhée liée à la rougeole et déterminer l'efficacité, par rapport au coût, de la vaccination antirougeoleuse en tant que stratégie visant à réduire la mortalité due aux maladies diarrhéiques.

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CH 3.3

Research Recherche

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Diarrhoeal disease control: reviews of potential interventions

R. G. FEACHEM,[1] R. C. HOGAN,[2] & M. H. MERSON[2]

Diarrhoeal diseases are a major cause of sickness and death among young children in most developing countries. Since effective interventions to control these diseases are available, they are a priority target for the primary health care programmes being planned or implemented in many countries. Governments and international agencies, including the World Health Organization, have emphasized oral rehydration as an effective intervention for reducing diarrhoeal disease mortality. Other interventions are, however, needed to reduce morbidity, to reduce mortality not averted by oral rehydration, and to develop a multifaceted approach in which oral rehydration is one of several anti-diarrhoea measures being implemented simultaneously with mutally reinforcing and complementary impacts. This paper presents a classification of potential interventions for the control of diarrhoeal disease morbidity and/or mortality among children under 5 years of age and introduces a series of reviews of these interventions. The first of these reviews, on measles immunization, also appears in this issue of the Bulletin of the World Health Organization.

The concept of primary health care involves the delivery of a package of curative and preventive health services at the community level. Various health service needs have to be satisfied but, owing to manpower, budgetary and other resource constraints, it is necessary to select those few that meet the priority health needs and are, at the same time, affordable. A number of approaches may be used to design an appropriate primary care package in a specific country or region. A rational approach is first to define the major health problems and then select the most cost-effective means of ameliorating them. This approach has been discussed fully elsewhere (*1*, *2*).

Identifying and ranking the major health problems may be done, in defined age groups, by the use of objective measures of the burden of death or illness attributable to specific diseases. If this is done, diarrhoeal diseases emerge in most developing countries as a major cause of sickness and death in young children (*2*). Recent estimates show that diarrhoeal diseases cause nearly 5 million deaths per year in children under 5 years old in developing countries (excluding China) where in every 100 children in this age group there are, on average, 220 diarrhoeal episodes and 1.4 deaths from diarrhoea every year (*3*). For a health problem to be a target for selective primary health care, it must not only be a major cause of sickness and death but it must also be controllable at a reasonable cost. Diarrhoeal disease mortality can be effectively reduced at reasonable cost by oral rehydration (*4*) and possibly other measures.

INTERVENTIONS FOR DIARRHOEAL DISEASE CONTROL

In circumstances where diarrhoeal diseases have been identified as a priority health problem, and a commitment has been made to combat the problem, it is necessary to decide how to reduce the mortality and

[1] Reader in Tropical Public Health Engineering, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, England.

[2] Diarrhoeal Diseases Control Programme, World Health Organization, 1211 Geneva 27, Switzerland. Requests for reprints should be sent to Dr M. H. Merson.

morbidity they cause. The funds available in many countries for the total primary health care package are in the order of only US$ 1–5 per capita per year, and only a proportion of this may be devoted to the control of diarrhoeal diseases. How should this amount be spent?

This is not a new question. The Fifth Caribbean Health Ministers' Conference, meeting in Dominica in 1973, called for a plan of action against diarrhoeal diseases and malnutrition in children under 2 years old. A group of experts was convened and recommended a 10-point programme designed to achieve specified reductions in mortality and morbidity.[a] This plan of action, although embracing several important aspects of diarrhoea control, did not provide guidance to governments on the comparative cost-effectiveness of the many different interventions recommended.

More recently, Walsh & Warren (*2*) identified diarrhoeal diseases as a priority target for selective primary health care and emphasized oral rehydration as the key intervention for the reduction of diarrhoeal disease mortality. Chen (*5*) drew attention to the importance of diarrhoea morbidity and to the need for interventions (other than oral rehydration) that are specifically addressed to this facet of the overall diarrhoea problem.

It is widely agreed that oral rehydration, delivered within a primary health care programme, is an effective and relatively inexpensive intervention for the reduction of mortality due to dehydrating diarrhoeas. Other interventions are also required, however, for three main reasons. First, like all health services delivered at the community level, oral rehydration programmes face operational constraints that may militate against the achievement of their full potential impact. Second, oral rehydration is of limited use in the treatment of chronic or dysenteric diarrhoeas and, in areas of the world where these are responsible for a considerable proportion of diarrhoeal disease mortality, the effect of oral rehydration programmes on the overall mortality from diarrhoeal diseases may be modest. Third, oral rehydration can be expected to have little or no impact on diarrhoea morbidity rates. A multifaceted strategy is therefore preferable, in which oral rehydration is but one of several anti-diarrhoea measures being implemented simultaneously, with mutually reinforcing and complementary impacts.

The Diarrhoeal Diseases Control (CDD) Programme of the World Health Organization has, since its inception in 1978, advocated the following four-part strategy for diarrhoea control:

— improved case management, with particular emphasis on the early use of oral rehydration therapy in acute diarrhoea and on appropriate feeding during illness and convalescence;

— improved maternal and child health care, with particular emphasis on breast-feeding, weaning practices, personal and domestic hygiene, and maternal nutrition;

— improved use and maintenance of drinking-water and sanitation facilities, and improved food hygiene;

— detection and control of epidemics.

In the first years of the CDD programme, greatest emphasis was placed upon oral rehydration as the primary intervention for reducing diarrhoeal disease mortality among young children (*3*). The CDD programme has developed detailed recommendations for oral rehydration therapy[b] and the production of oral rehydration salts,[c] and has worked with governments of Member countries in the planning, implementation and evaluation of oral rehydration and other diarrhoea control measures.[d] With the implementation of CDD programmes in over 35 countries, it is now appropriate to supplement the emphasis on oral rehydration by developing, in detail, other interventions for diarrhoea control and undertaking the necessary field research and evaluation to establish their feasibility and cost-effectiveness.

The CDD programme has therefore undertaken a systematic and comprehensive review of the effectiveness, feasibility and cost of the many possible anti-diarrhoea interventions available for the reduction of morbidity and/or mortality among children under 5 years of age. A classification of such interventions is shown in Table 1. Its purpose is to guide and systematize the process of review and not to provide a recommendation for diarrhoeal diseases control. Each intervention listed in Table 1, and possibly others that may subsequently be proposed, will be reviewed using a standard format which places emphasis on information concerning the effectiveness of the intervention. If the intervention is known or believed to be effective, available data on its feasibility and cost are also presented.

As a result of these reviews, each intervention listed in Table 1 will be assigned to one of three categories, each having different requirements for follow-up action by the CDD programme. First are interventions that are clearly shown to be effective, feasible and affordable. For these, the next step will be for

[a] *Strategy and plan of action to combat gastroenteritis and malnutrition in children under two years of age.* Report of a Technical Group Meeting on Malnutrition and Gastro-enteritis, St Vincent, 8–11 January 1974 (Unpublished document).

[b] *A manual for the treatment of acute diarrhoea.* Unpublished document WHO/CDD/SER/80.2, 1980.

[c] *Guidelines for the production of oral rehydration salts.* Unpublished document WHO/CDD/SER/80.3, 1980.

[d] *Manual for the planning and evaluation of national diarrhoeal diseases control programmes.* Unpublished document WHO/CDD/SER/81.5, 1981.

Table 1. Potential interventions for reducing diarrhoeal morbidity or mortality among children under five years of age

I. By case management

- A. *Oral rehydration therapy*
  1. Administration of oral rehydration in the home.
  2. Administration of oral rehydration at a medical facility.
- B. *Non-oral rehydration therapy*
  1. Administration of rehydration by intravenous or other routes at a medical facility.
- C. *Appropriate feeding*
  1. Promoting the appropriate feeding of children during diarrhoeal illness and convalescence.
- D. *Chemotherapy*
  1. Administration of therapeutic agents in the home.
  2. Administration of therapeutic agents at a medical facility.

II. By increasing host resistance to infection and/or illness and/or death

- A. *Maternal nutrition*
  1. Improving prenatal nutrition to reduce the incidence of low birth-weight.
  2. Improving prenatal and postnatal nutrition to improve the quality of breast milk.
- B. *Child nutrition*
  1. Promoting exclusive breast-feeding up to age 4–6 months and partial breast-feeding thereafter.
  2. Improving weaning practices for children aged 4–18 months (introducing non-milk foods not later than the sixth month, continuing breast-feeding for as long as possible, and using nutritious and locally available weaning foods).
  3. Supplementary feeding to improve the nutritional status of children aged 6–59 months.
  4. Promoting the use of growth charts by mothers as an aid to proper child nutrition and child care.
- C. *Immunization*
  1. Rotavirus and/or cholera immunization (when effective and tested vaccines are available) of the child and/or mother.
  2. Measles immunization to reduce measles-associated diarrhoea.
- D. *Chemoprophylaxis*
  1. Chemoprophylaxis of children at special risk, such as contacts of known cases, to reduce the incidence and/or severity of diarrhoea.

III. By reducing transmission of the pathogenic agents of diarrhoeal diseases

- A. *Water supply and excreta disposal*
  1. Constructing water supplies that improve the quality and availability of water for domestic purposes, and improved excreta disposal facilities; and providing the necessary educational support to ensure use and maintenance of these new facilities.
- B. *Personal and domestic hygiene*
  1. Promoting specific features of personal and domestic hygiene, such as hand-washing, by appropriate educational campaigns.
- C. *Food hygiene*
  1. Promoting improved practices for the preparation and storage of foods, both commercially and in the home, and especially emphasizing the hygienic preparation of weaning foods.
- D. *Control of zoonotic reservoirs*
  1. Control of infection of domestic and farm animals by pathogens causing diarrhoea in man.
- E. *Fly control*
  1. Control of flies, especially flies breeding in association with human or animal faeces.

IV. By controlling and/or preventing diarrhoea epidemics

- A. *Epidemic surveillance, investigation and control*
  1. Improving the ability to identify and investigate an epidemic early in its course and the capacity to implement effective control activities.

the CDD programme to develop detailed guidelines for their implementation within national primary health care programmes and to promote any operational research needed to improve their delivery or impact. Second are interventions for which there is good theoretical evidence of effectiveness but insufficient field experience to predict impacts precisely or to judge feasibility and cost. For these the next step will be for the CDD programme to promote field research designed to fill the gaps in knowledge. The results of this research will determine whether these category 2 interventions are moved to category 1 or category 3. Third are interventions which are shown to be either ineffective, unfeasible or too costly. These interventions will not be recommended by the CDD programme as important elements of diarrhoeal dis-

ease control activities or priorities for diarrhoeal disease research. It is hoped that this review will help focus the attention of governments, researchers and international agencies on a few interventions of known or suspected effectiveness which, if implemented along with oral rehydration therapy, could markedly reduce the rates of both morbidity and mortality due to diarrhoeal diseases among young children.

Reviews of some of the interventions listed in Table 1 will be published in the *Bulletin of the World Health Organization*. The first of these is published in this issue (pp. 641–652) and deals with measles immunization as an intervention for diarrhoeal disease control (II.C.2 in Table 1). It is hoped to publish in forthcoming issues of the *Bulletin* reviews on supplementary feeding (II.B.3), breast-feeding (II.B.1), and personal and domestic hygiene (III.B.1). Readers having suggestions to make on the classification of potential interventions in Table 1, or on the individual reviews as they are published, are invited to write to the Programme Manager, Diarrhoeal Diseases Control Programme, World Health Organization, 1211 Geneva 27, Switzerland.

RÉSUMÉ

ANALYSE DES MODES D'INTERVENTION POSSIBLES DANS LA LUTTE CONTRE LES MALADIES DIARRHÉIQUES

Les maladies diarrhéiques constituent dans la plupart des pays en développement l'une des causes principales de morbidité et de mortalité chez les jeunes enfants. Du fait que l'on dispose pour lutter contre ces maladies de modes d'intervention efficaces, ils doivent représenter un objectif prioritaire des programmes de soins de santé primaires planifiés ou mis en œuvre dans nombre de pays. Des gouvernements et des organismes internationaux, y compris l'Organisation mondiale de la Santé, ont souligné que la réhydratation par voie orale était une intervention essentielle pour réduire la mortalité due aux maladies diarrhéiques. Mais il est nécessaire cependant de disposer d'autres façons d'intervenir encore pour diminuer la morbidité, abaisser le nombre de décès que ne peut empêcher la réhydratation par voie orale et mettre au point une approche conjuguée, dans laquelle la réhydratation orale représente l'une seulement des diverses mesures antidiarrhéiques appliquées simultanément et dont les effets se renforcent et se complètent mutuellement. L'article qui suit contient une classification des interventions possibles pour lutter contre la morbidité et/ou la mortalité dues aux maladies diarrhéiques chez les enfants de moins de 5 ans, et annonce le début d'une série d'analyses de ces stratégies, dont la première — sur la vaccination antimorbilleuse — est publiée dans ce même numéro du *Bulletin de l'Organisation mondiale de la Santé*.

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Interventions for the control of diarrhoeal diseases among young children: promotion of breast-feeding

R. G. FEACHEM[1] & M. A. KOBLINSKY[2]

The literature on the relative risks of diarrhoea morbidity to infants on different feeding modes suffers from several methodological problems. Thirty-five studies from 14 countries were reviewed; 83% of studies found that exclusive breast-feeding was protective compared to partial breast-feeding, 88% that exclusive breast-feeding was protective compared to no breast-feeding, and 76% that partial breast-feeding was protective compared to no breast-feeding. When infants receiving no breast milk are contrasted with infants on exclusive or partial breast-feeding, the median relative risks are 3.0 for those aged 0–2 months, 2.4 for those aged 3–5 months, and 1.3–1.5 for those aged 6–11 months. Above 1 year of age no protective effect of breast-feeding on diarrhoea morbidity is evident. When infants receiving no breast milk are contrasted with those on exclusive breast-feeding, median relative risks are 3.5–4.9 in the first 6 months of life. The literature does not suggest that the relative risks of diarrhoea morbidity for bottle-fed infants are higher in poor families than in more wealthy families. The protective effects of breast-feeding do not appear to continue after the cessation of breast-feeding. There is evidence of considerably increased diarrhoea severity among bottle-fed infants.

There is a limited, and mostly pre-1950, literature on the relative risks of diarrhoea mortality to infants on different feeding modes. Nine studies from 5 countries were reviewed, most of which showed that breast-feeding protects substantially against death from diarrhoea. When infants receiving no breast milk are contrasted with those on exclusive breast-feeding, the median relative risk of death from diarrhoea during the first 6 months of life is 25. When partially and exclusively breast-fed infants are contrasted, the median relative risk of death from diarrhoea is 8.6.

Breast-feeding can be promoted by changes in hospital routine and by giving information and support to mothers. A review of 21 studies from 8 countries shows that, by such promotion, the most likely reductions in the prevalence of non-breast-fed infants are 40% among infants aged 0–2 months, 30% among those aged 3–5 months, and 10% among those between 6 months and 1 year old. Theoretical calculations based on these data show that such promotion can reduce diarrhoea morbidity rates by 8–20% and diarrhoea mortality rates by 24–27% in the first 6 months of life. For children aged 0–59 months, diarrhoea morbidity rates would be reduced by 1–4% and mortality rates by 8–9%. A recent study in Costa Rica has documented a substantial impact of breast-feeding promotion on neonatal diarrhoea morbidity and mortality, and on diarrhoea morbidity in infants aged 0–5 months. The Costa Rican data show good agreement with the theoretical computations presented in this paper.

Several important aspects of breast-feeding and diarrhoea remain to be clarified by research. However, the need for this research should not delay action to promote breast-feeding and to monitor its effects upon feeding practice and upon diarrhoea.

The long debate on the merits of breast-feeding initially focused on the differences in mortality rates between breast-fed and bottle-fed infants. Since about 1930, and especially since 1955, increased attention has been paid to differential morbidity rates. Some studies on mortality and morbidity in relation to feeding mode singled out particular infectious causes of death or illness—most commonly, diarrhoeal and respiratory diseases. The literature on the relationships between breast-feeding and

[1] Reader in Tropical Public Health Engineering and Head of Department of Tropical Hygiene, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, England. Requests for reprints should be sent to Programme for Control of Diarrhoeal Diseases, World Health Organization, 1211 Geneva 27, Switzerland.

[2] Scientific Coordinator, International Centre for Diarrhoeal Disease Research in Bangladesh, Dhaka, Bangladesh.

diarrhoea is now substantial and permits an assessment of breast-feeding promotion as an intervention for the reduction of diarrhoea morbidity or mortality in infants. Several recent studies and reviews of breast-feeding provide a useful background to the present, more focused analysis (*2*, *17*, *47*, *51*, *64*, *66*, *81*, *86*)[a-c] of the role of breast-feeding promotion in diarrhoeal disease control. This review is the third in a series of reviews of potential anti-diarrhoea interventions now being published in the *Bulletin of the World Health Organization* (*19–21*).

EFFECTIVENESS

For breast-feeding promotion to be an effective diarrhoea control intervention, it must be true that:

either

breast-fed infants have reduced diarrhoea morbidity rates, mortality rates, or severity	*hypothesis 1*

and

the prevalence of breast-fed infants can be increased by appropriate promotional activities	*hypothesis 2*

or

the promotion of breast-feeding can reduce diarrhoea morbidity rates, mortality rates, or severity in infants	*hypothesis 3*

Most of the literature on this topic is addressed to hypothesis 1 or 2. The potential effectiveness of breast-feeding promotion would be suggested by a demonstration either of the correctness of hypotheses 1 and 2 or of the correctness of hypothesis 3. The evidence for and against these hypotheses is examined below.

[a] EVENSEN, S. *Relationship between infant morbidity and breast-feeding versus artificial feeding in industrialized countries: a review of the literature.* Copenhagen, WHO Regional Office for Europe, 1982 (unpublished document ICP/NUT 010/6).

[b] *Joint WHO/UNICEF meeting on infant and young child feeding*, Geneva, 1979 (unpublished document).

[c] WHO/UNICEF. *Infant and young child feeding: current issues*, Geneva, 1981 (unpublished document).

Hypothesis 1. *Breast-fed infants have reduced diarrhoea morbidity rates, mortality rates, or severity*

Definitions

A review of breast-feeding and diarrhoeal disease rates requires clear-cut definitions of the various feeding modes that are to be contrasted. The number of feeding modes defined should be small (say, 3 to 5) in order to increase the sample size of infants on each feeding mode and in order that the operational significance of the comparisons will be apparent. However, to assign all of the many permutations of infant feeding practice to only 3–5 categories inevitably introduces a degree of imprecision to the definitions. In this review the following three categories have been adopted:

—exclusive breast-feeding, which applies to infants receiving only breast milk (and is thus not usual in infants over 6 months old);

—no breast-feeding, which applies to infants receiving no breast milk;

—partial breast-feeding, which applies to infants who receive breast milk plus other milk or foods.

The feeding modes described in the literature are assigned to one of these three categories. In several studies the feeding modes have not been clearly defined or do not correspond to any of the categories listed above. In these cases, the feeding mode is designated so as to minimize the computed protective effect of breast-feeding.

Methodological problems

The studies on breast-feeding and diarrhoea reviewed here made use of different methods for the collection and analysis of their data. Studies that were judged to have serious methodological flaws were rejected but the quality of those that were included varies widely. The most commonly encountered problem other than definition of feeding mode (see above) was failure to control possible confounding variables. The age of the infant is a confounding variable encountered in all the studies; older infants are less likely to be exclusively breast-fed than younger infants and also have different diarrhoeal disease rates for reasons other than feeding mode. Emphasis has therefore been placed here on studies that analyse breast-feeding and diarrhoea rates by narrow age ranges (e.g., 0–2 months, 3–5 months, etc.); studies that examine a wider age range of infants, e.g., aged 0–11 months, are judged to be of little value.

A second common set of confounding variables is socioeconomic status and child care. Mothers who breast-feed may be more or less educated and

wealthy, and may take more or less care of their child than other mothers. Two distinct patterns emerged from the studies that analysed the effect of these confounding variables. In some poor communities, especially in developing countries and in the developed countries before 1930, breast-feeding was more common among lower socioeconomic strata. In such communities the confounding socioeconomic variables tend to increase the diarrhoea rates and therefore minimize the apparent protective effect of breast-feeding. In an uncontrolled study in such communities the protection afforded by breast-feeding may be underestimated. In certain more prosperous communities, especially in developed countries, breast-feeding is at present more common among the middle classes because it is fashionable. Here the confounding socioeconomic variables tend to decrease the diarrhoea rates and thus an uncontrolled study may overestimate the protective effect of breast-feeding. Several of the more recent studies that were reviewed controlled for confounding socioeconomic and child care variables, and such control should be regarded as essential for any future studies of breast-feeding and diarrhoea. These and other methodological problems inherent in studies of breast-feeding and health are reviewed elsewhere (*9*, *70*, *84*).[d]

Mechanisms of protection

If breast-fed infants experience less diarrhoeal illness or death than other infants, it may be due to one or more of the following factors:

— the immunological and antimicrobial properties of breast milk;

— the "bifidus factor" (exclusively breast-fed infants have an intestinal flora composed largely of Gram-positive anaerobic bacteria (*Bifidobacterium* species), which may inhibit colonization by Gram-negative facultative species such as *Escherichia coli*);

— infants receiving bottle-milk feeds are at risk from contamination of the milk, the bottle, or the teat, and infants receiving solid foods are at risk from contamination of the food (these risks may apply especially to bacterial pathogens that multiply in milk and some foods);

— breast-fed infants may have a better nutritional status than other infants, and thus a lesser risk of death from diarrhoea.

The protective mechanisms of breast-feeding are a complex subject, in which there is substantial ongoing research. This is especially true of the first of the four items listed above. It is probable that the mechanisms of protection, and their relative importance, vary by pathogen and by the age of the infant. It is not the purpose of this paper to review the literature on protective mechanisms, and the interested reader is referred to other publications (*3*, *4*, *14*, *17*, *26*, *30*, *33*, *40–42*, *55*, *58*, *60*, *65*, *83*).

Morbidity

Annex 1 lists 35 studies in 14 countries from which the relative risk of diarrhoeal illness for infants on one feeding mode, compared to infants on another feeding mode, can be computed. Both methods and findings vary greatly among these studies. For partial breast-feeding compared to exclusive breast-feeding, 30 relative risks are computed of which 25 (83%) are > 1. For no breast-feeding compared to exclusive breast-feeding, 25 relative risks are computed of which 22 (88%) are > 1. For no breast-feeding compared to partial breast-feeding, 45 relative risks are computed of which 34 (76%) are > 1. Thus the pooled results from 35 studies indicate that in most circumstances breast-feeding protects against diarrhoea morbidity. More analysis on these pooled data is not useful since the results are strongly influenced by the age of the infants under study.

The age-specific relative risks derived are summarized in Fig. 1 and 2, which show clearly the effect of age. When infants receiving no breast milk are contrasted with infants on exclusive or partial breast-feeding (Fig. 1), the median relative risks are 3.0 for ages 0–3 months, 2.4 for ages 3–5 months,[c] and 1.3–1.5 for ages 6–8 and 9–11 months. Above 1 year of age, no protective effect of breast-feeding on

[c] The 0–3-months age group includes studies of both the 0–2-months group and the 0–3-months group. This age group therefore overlaps by one month (month 3) with the 3–5-months age group. These remarks also apply to Fig. 1 and 2.

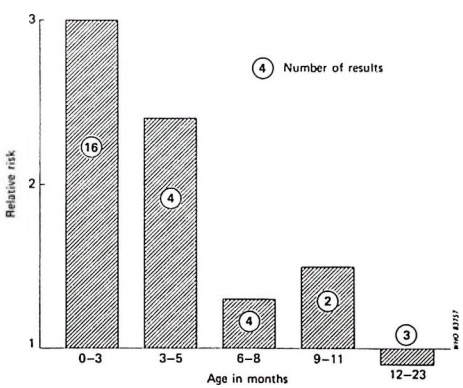

Fig. 1. Median relative risks of diarrhoea morbidity for infants receiving no breast-feeding compared to infants with partial or exclusive breast-feeding (data from Annex 1).

[d] See footnote *a* on page 272.

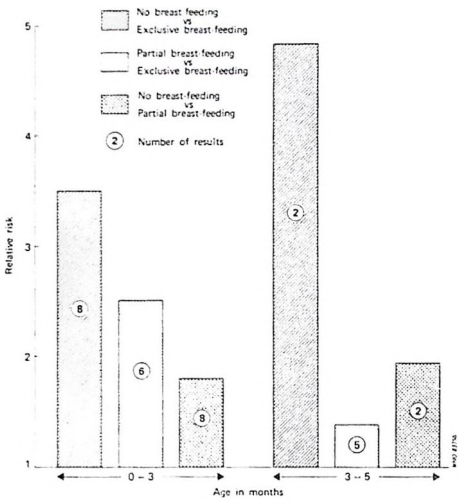

Fig. 2. Median relative risks of diarrhoea morbidity by feeding mode (data from Annex 1).

diarrhoea morbidity is evident. When infants receiving no breast milk are contrasted with those on exclusive breast-feeding (Fig. 2), the median relative risks are 3.5–4.9 in the first 6 months of life. Beyond 6 months of age, exclusive breast-feeding is not a nutritionally recommended feeding mode and may be a risk factor, rather than a protective factor, for diarrhoea. This possibility is illustrated by the data from Ethiopia and Uganda (Annex 1).

It is possible that the relative risks of diarrhoea for bottle-fed infants are greatest in families of lowest socioeconomic status where diarrhoea incidence is high and nutritional status is low, and where there are many opportunities for the contamination of bottle milk. The data in Annex 1 were analysed (not shown) to test this possibility and gave no grounds for supposing that the relative risks of diarrhoea for bottle-fed infants are lower in more wealthy families. Breast-feeding appears to protect against diarrhoea irrespective of the levels of hygiene. This suggests either that the main protective mechanisms are the immunological and antimicrobial properties of the breast milk together with the "bifid" flora of the gut or that contamination of bottle milk is an important cause of infant diarrhoea even in families of upper and middle socioeconomic status. The possible lack of association between the relative protection afforded by breast-feeding and socioeconomic status should be further studied.

The discussion above deals only with the protective effects of a particular feeding mode during the period when this feeding mode is applied. It is conceivable that breast-feeding confers some protection against diarrhoea after breast-feeding has been discontinued. Few studies present data that allow this possibility to be analysed. The findings of Ferguson et al. (*23*) in New Zealand are summarized in Table 1. All infants described in Table 1 had ceased breast-feeding and their period prevalences of diarrhoea are compared according to their past experience of breast-feeding. The data are weakened by the use of period prevalence rather than incidence but, none the less, the results do not suggest that a longer duration of breast-feeding was associated with a lower period prevalence of diarrhoea. This cessation of protection after discontinuation of breast-feeding has been reported also in studies of all significant illness episodes (*9*) and of total hospital admissions (*15*).

Severity

Only a few studies provide data from which the relationship between breast-feeding and diarrhoea severity may be assessed. Table 2 summarizes 5 studies of case-fatality ratios. Four of these (from England in the 1930s, USA in the 1920s, and Rwanda recently) show major differences in case-fatality ratios by feeding mode. These results could be confounded by other clinical problems of the children who died; those not breast-fed could have been undernourished or chronically ill, for instance. The data from Birmingham, England, in the 1930s (*73*) show that the prevalences of undernutrition (< 80%

Table 1. Period prevalence of treated diarrhoeas and all diarrhoeas in specified age groups, by duration of previous breast-feeding[a]

Age group (months, inclusive)	Duration of previous exclusive breast-feeding (months)	Period prevalence (%)	
		Treated diarrhoeas[b]	All diarrhoeas[c]
4–11	0	22	44
	0–3	25	48
12–23	0	29	63
	0–3	32	64
	4–7	31	64
	8–11	29	65

[a] Data from Ferguson et al. (*23*).

[b] Diarrhoeas reported to a medical practitioner or hospital for treatment.

[c] All diarrhoeas, including those managed at home.

Table 2. Case–fatality ratios for diarrhoea cases in four countries, by feeding mode

Country and place	Date of study	Socio-economic status	Age group (inclusive)	Total number of diarrhoea cases (deaths)	Case-fatality ratios (%)			Ratio of case-fatality ratios (No BF/ Part BF)	Reference
					Excl. BF[a]	Part BF[a]	No BF[a]		
Canada									
Toronto[b]	1939	?	0–11 mo.	314 (46)		14	15	1.1	*13*
England									
Liverpool	1936	Lower/ middle	3–26 wk	130 (9)		5	9	1.8	*69*
Birmingham[b]	?	?	0–9 mo.	500 (240)		26	77	3.0	*73*
Rwanda									
Kigali[b]	1977–78	?	0–23 mo.	849 (95)		7	22	3.1	*50*
USA									
Chicago	1924–29	Lower	0–3 mo.	1877 (22)	0.6	0.9	20	22	*35*
			4–8 mo.			0.3	2	6.7	*36*

[a] For definitions of feeding modes, see footnote *b* to Annex 1.

[b] Study of hospitalized diarrhoea cases only.

weight-for-age) among non-breast-fed infants who died of diarrhoea, and among all diarrhoea cases, were 41% and 37% respectively, suggesting that the apparent effect of feeding mode on case–fatality ratio (Table 2) was not confounded by malnutrition. Grulee (*35*), commenting on the Chicago (1924–29) study, wrote that "1924 to 1929 were the years of plenty" and that "undernutrition does not enter into the picture". The Chicago study used data from the surveillance of over 20 000 infants. Such data are less likely to be confounded by undernutrition, and much less likely to be confounded by chronic illness, than data derived from hospitalized cases only.

An investigation of shigellosis in Bangladesh (*77*) found that severity was related to feeding mode. Breast-fed and non-breast-fed children under 2 years old with shigellosis were compared; among the breast-fed group, fewer required intravenous therapy (16% vs 38%) and fewer were admitted as inpatients (5% vs 19%).

Breast-feeding may play a role in reducing the nutritional consequences of diarrhoea episodes in young children. A study of children aged 6–35 months, hospitalized with acute watery diarrhoea in Bangladesh, showed that those being breast-fed had calorie and protein intakes (per kg of body weight) 1.5 and 2.5 times greater, respectively, than those not breast-fed (*45*).

More information is required on the effects of feeding mode on diarrhoea severity. Such studies should control for age, nutritional status, and chronic illness and should investigate the severity of diarrhoeas of known etiology.

Mortality

Annex 2 lists 9 studies in 5 countries from which the relative risks of diarrhoea mortality for infants on one feeding mode, compared to infants on another feeding mode, can be computed. The data are less extensive than those on morbidity (Annex 1) and do not permit such detailed analysis by age. For partial breast-feeding compared to exclusive breast-feeding, 7 relative risks are computed, ranging in value from 1 to 10. For no breast-feeding compared to exclusive breast-feeding, 13 relative risks are computed, ranging in value from 3 to 43. For no breast-feeding compared to partial breast-feeding, 9 relative risks are computed, ranging in value from 2 to 19. Thus the pooled results from 9 studies suggest that breast-feeding may protect substantially against death from diarrhoea.

The age-specific relative risks of diarrhoea mortality, from 2 studies in which age-specific analysis is possible, are presented in Fig. 3. The relative risk of death from diarrhoea for non-breast-fed infants is greatly increased in the early months of infancy compared to the later months. The relative risks of diarrhoea mortality for infants 0–5 months old are summarized in Fig. 4 by feeding mode. When infants receiving no breast milk are contrasted with those on exclusive breast-feeding the median relative risk of death from diarrhoea during the first 6 months of life is 25. When infants on mixed feeding modes (partial breast-feeding) are contrasted with those on exclusive breast-feeding the median relative risk of death from diarrhoea is 8.6. It must be cautioned that these

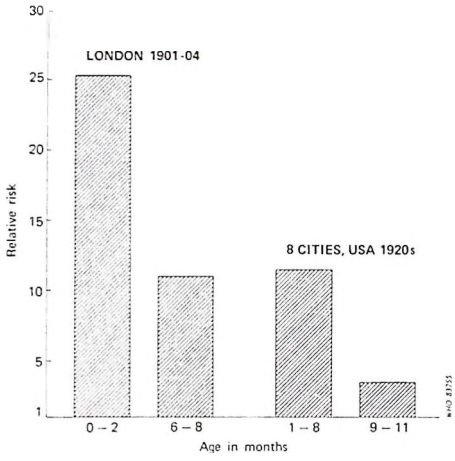

Fig. 3. Relative risks of diarrhoea mortality for infants receiving no breast-feeding compared to infants exclusively breast-fed (data from Annex 2).

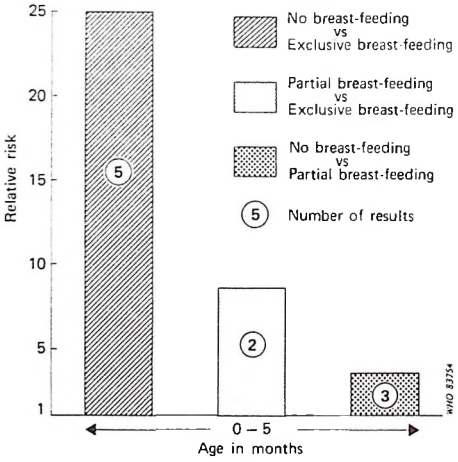

Fig. 4. Median relative risks of diarrhoea mortality by feeding mode (data from Annex 2, including studies of 0–2, 3–5 and 0–5-months age groups).

results are derived from only two studies (*62*, *69*) and mainly from the study of Newman (*62*). Comparison of Fig. 2 and 4 shows that the relative risks of diarrhoea mortality by feeding mode are 2–6 times greater than those of diarrhoea illness. This implies a similar difference in the case-fatality ratios by feeding mode.

Table 2 shows the ratios of no breast-feeding to partial breast-feeding case-fatality ratios to be 1.1, 1.8, 3.0, 3.1, 6.7 and 22.

As with the case-fatality ratios (Table 2), the mortality rates by feeding mode (Annex 2) could be confounded with undernutrition or chronic illness. A factor that causes the abandonment of breast-feeding, such as a chronic illness, could also increase the risk of death from diarrhoea. Four studies listed in Annex 2 controlled for these, or related factors, or excluded infants who were disadvantaged from birth owing to prematurity, low birth-weight, or congenital defects. In addition, four of the studies in Annex 2 derived their mortality rates from records of over 100 deaths from diarrhoea. With sample sizes of this magnitude it is unlikely that rare events such as chronic illness would substantially alter the computed effect of feeding mode.

Despite these comments, the data from which to draw conclusions about the relative risks of diarrhoea mortality by feeding mode are limited in extent and quality. The studies are old (only one since 1947); all except one are from what are now wealthy and temperate countries (Canada, England, Sweden, and the USA); they provide poor breakdown of mortality rates by age; and they do not adequately control for potentially confounding variables. The age of the studies is of concern first because their designs are inadequate as judged by today's epidemiological standards, and secondly because the non-breast-fed infants were not receiving modern infant milk formulae. The importance of this last point is uncertain. Of the four potential protective mechanisms listed above, only nutritional status is likely to be affected by the type of breast-milk substitute.

Reliable data on the effect of feeding mode on diarrhoea mortality rates in developing countries today are not available. The collection of such data through correctly designed studies is a priority item for research programmes in both diarrhoeal diseases and maternal and child health. Evidence that such studies will find a significant relative risk of diarrhoea mortality among bottle-fed infants comes from studies of overall infant mortality by feeding mode. For instance, a study in north-eastern Brazil found that, when numerous confounding variables were controlled, children who were never breast-fed were 1.7 times more likely to die in infancy than other children (*29*).

Etiology-specific diarrhoea and breast-feeding

There is a growing literature on substances in human colostrum and milk that act against specific agents of diarrhoea. Most attention has been focused on antibodies against rotavirus (*71*, *72*, *90*), antibodies against *Escherichia coli* and its toxins (*1*, *28*,

48), and antibodies against *Vibrio cholerae* and its toxin (*53*, *72*).

Little is known of the relationships between feeding mode and the epidemiology of diarrhoeas of known etiology. High relative risks of cholera in Bahrain, and of salmonellosis in Arkansas, USA, in infants receiving no breast milk have been documented (Annex 1). In a study of 5-day-old babies in London, England, the prevalences of rotavirus infection among breast-fed and non-breast-fed infants were 22% and 58% respectively (*6*). Only 14% of infected breast-fed infants excreted $> 10^9$ virus particles per gram of faeces, compared to 52% of non-breast-fed infected infants. In a study of children under 1 year old, hospitalized with diarrhoea in Mexico City, Mexico, 5% of those with rotavirus infection were breast-fed compared to 16% of those with other diarrhoeas (*16*). In a study of children under 2 years old with diarrhoea in Dhaka, Bangladesh, the proportion who were breast-fed was 59% in those with shigellosis compared to 78% in those with other diarrhoeas (*77*). A similar association with breast-feeding was not found for the other common enteric pathogens.

This information is incomplete and partially contradictory. It is uncertain whether the protection against diarrhoea morbidity and mortality associated with breast-feeding (Fig. 1-4) extends to all diarrhoeas or is due to high protection against some agents and low protection against others. Studies on feeding mode in relation to the incidence and severity of specific diarrhoeas are needed to clarify the situation and to guide intervention policy towards geographical areas in which breast-feeding may be especially important.

Hypothesis 2. *The prevalence of breast-fed infants can be increased by appropriate promotional activities*

The most recent and comprehensive account of patterns of breast-feeding is provided by a WHO collaborative study of 22 857 mothers in 9 countries (*86*). The reader concerned with the details of breast-feeding trends and practices should study this report. Simplified data on three contrasting patterns of breast-feeding (dubbed here patterns A, B and C) have been abstracted and are set out in Table 3. Pattern A may be found in relatively urbanized and wealthy communities in developing countries and in some developed countries. It is a pattern where non-breast-feeding is prominent and it may be an increasingly common pattern in many developing countries, especially in urban areas. Pattern C is a pattern of predominant breast-feeding and may be found in many poor and traditional societies in developing countries.

Table 3. Three contrasting patterns for breast-feeding[a]

Pattern of breast-feeding[b]	Countries and the socioeconomic strata of the population studied				Type of feeding[c]	Prevalence (%) of breast-feeding by age of infant		
	All strata	Upper/ middle	Urban poor	Rural poor		0-2 mo.	3-5 mo.	6-11 mo.
A	Hungary Sweden	Chile Ethiopia Guatemala Nigeria Philippines	Chile		Excl. BF	30	10	0
					Part BF	45	35	15
					No BF	25	55	85
B		India Nigeria	Guatemala Philippines	Chile Philippines	Excl. BF	50	30	5
					Part BF	40	45	55
					No BF	10	25	40
C		Zaire	Ethiopia India Nigeria Zaire	Ethiopia Guatemala India Nigeria Zaire	Excl. BF	75	50	20
					Part BF	25	45	70
					No BF	0	5	10

[a] All data drawn from Fig. 3 and Tables 3 and A5 of the WHO breast-feeding study (*86*). The data have been greatly simplified for the purposes of this analysis on breast-feeding and diarrhoea; for the details of breast-feeding patterns, please consult the full report (*86*).

[b] Patterns A, B, and C may be expected in 'modern', 'transitional', and 'traditional' communities, respectively. It is assumed that these communities suffer low, medium, and high incidences of diarrhoea, respectively (see Tables 6 and 8).

[c] For definitions of feeding modes, see footnote *b* to Annex 1.

Pattern B is intermediate between patterns A and C and may be found in societies that are transitional, in terms of both social norms and wealth. This three-part categorization of breast-feeding patterns is a considerable simplification of the actual global picture as described by WHO (*86*). This simplification is necessary for the computations on breast-feeding promotion and diarrhoea reduction that follow below. The reader interested in a specific community, where the breast-feeding pattern is known, can insert local data in place of those given in Table 3 and repeat the computations.

In some countries, most notably certain developed countries (with breast-feeding pattern A, Table 3), growing public awareness of the advantages of breast-feeding has caused substantial increases in the prevalence of breast-fed infants over a short time period (*64*). In Oslo, Norway, the prevalence of breast-feeding in infants aged 3 months was 14% in 1972–73 and 31% in 1974–75. In Copenhagen, Denmark, the median duration of breast-feeding doubled, from 2 to 4 months, between 1975 and 1977. In the USA the prevalence of infants who were only breast-fed rose from an all-time low of 26% in 1973 to 54% in 1980.

Promotion of breast-feeding can reduce the prevalence of non-breast-fed infants substantially. Table 4 summarizes the impact on breast-feeding of local breast-feeding promotions in Brazil, Czechoslovakia, England, Guatemala, Scotland, Singapore, Sweden, and the USA. Because of the very varied pre-promotion levels of breast-feeding, the impacts are expressed as percentage reductions in the prevalences of infants receiving no breast milk. In the computations (see below) the most likely reductions in the prevalences of non-breast-fed infants of various ages due to breast-feeding promotion are taken as 40% for the 0–2-months age group, 30% for the 3–5-months age group, and 10% for the 6–11-months age group (Table 4).

Table 4. The effectiveness of breast-feeding promotion programmes in reducing the prevalence of infants receiving no breast milk[a]

Age of infant (months, inclusive)	No. of results	% reduction in prevalence of non-breast-fed infants[b]	
		Range	Median
0–2	23	8–100	42
3–5	8	7–43	28
6–11	6	2–43	11

[a] Data derived from Winikoff & Baer (*85*) (summary of 20 studies in 8 countries) and from Hardy et al. (*43*).

[b] If the prevalences of non-breast-fed infants of a given age before and after the promotion are 70% and 50% respectively, the % reduction is 28.6%.

Hypothesis 3. *The promotion of breast-feeding can reduce diarrhoea morbidity rates, mortality rates, or severity in infants*

It is possible to calculate the theoretical impacts of breast-feeding promotion using the data assembled above on hypotheses 1 and 2. Median relative risks of both morbidity and mortality by age have been derived (Fig. 1-4), three contrasting patterns of breast-feeding have been described (Table 3), and the impact of breast-feeding promotion on breast-feeding has been reviewed (Table 4). The next step is to characterize the impact on breast-feeding of breast-feeding promotions having three levels of success: high impact, medium impact, and low impact. The consequences to breast-feeding patterns of these three levels of success are quantified in Table 5. The data on medium impact are derived from Table 4, while high and low impacts are assumed to influence twice and one half, respectively, of the proportion of target mothers.

From the data assembled in Fig. 1-4 and Tables 3-5 it is possible to compute the impact on age-specific diarrhoea morbidity and mortality rates of breast-feeding promotions with a given level of success (say, medium impact) in a community of known breast-feeding pattern (say, pattern A). For morbidity rates, key assumptions are presented in Table 6 and the reductions in age-specific diarrhoea morbidity rates are set out in Table 7. Considering breast-feeding promotions of medium impact, diarrhoea morbidity rates in the first 3 months of infancy may be reduced by 8–20%, and in the second 3 months of life by 9–17%, with the highest percentage reductions being achieved in communities where breast-feeding is initially least common (pattern A). Negligible reductions in diarrhoea morbidity rates are achieved among children over 6 months old. The computed reductions in total diarrhoea morbidity for the first five years of life are only 1–4%.

For mortality rates, key assumptions are presented in Table 8 and the reductions in age-specific diarrhoea mortality rates are set out in Table 9. Considering breast-feeding promotions of medium impact, diarrhoea mortality rates in the first 6 months of infancy may be reduced by 24–27%, and diarrhoea mortality rates for the first five years of life by 8–9%. Zero reductions in diarrhoea mortality rates are computed for children over 6 months old (Table 9) because of the conservative assumption of a relative risk of 1.0 for this age group (see footnote *d* to Table 8). The impacts on children aged 0–59 months are similar, whatever the initial level of breast-feeding (patterns A, B and C) because of the high diarrhoea mortality rates assumed for 0–5-month old infants in communities having breast-feeding pattern C (Table 8).

The computed morbidity and mortality reductions (Tables 7 and 9) for the total 0–59-months age group

Table 5. Data on the three levels of impact of breast-feeding promotion programmes[a]

Level of impact	Percentage changes in breast-feeding prevalence by age of infant and type of feeding						
	0–2 mo.			3–5 mo.			6–11 mo.[b]
	From No BF to Part BF[c]	From No BF to Excl. BF	From Part BF to Excl. BF	From No BF to Part BF	From No BF to Excl. BF	From Part BF to Excl. BF	From No BF to Part BF
High	40	40	80	30	30	60	20
Medium	20	20	40	15	15	30	10
Low	10	10	20	7.5	7.5	15	5

[a] *Explanation*: Consider a promotion with medium impact on the 0–2 mo. age group. It is assumed that the behaviour of 40% of the target mothers can be changed (Table 4). Thus 40% of Part BF switch to Excl. BF and 40% of No BF switch to Part BF or Excl. BF (20% to each mode). For low impact it is assumed that only 20% of target mothers can be influenced, while for high impact it is assumed that 80% of target mothers can be influenced.

[b] Since most authorities recommend supplementary feeding of infants over 5 months, it is assumed that the breast-feeding promotion would encourage Part BF and not Excl. BF in this age group.

[c] For definitions of feeding modes, see footnote *b* to Annex 1.

Table 6. Assumptions made in calculating the impact of breast-feeding promotions on diarrhoea morbidity

Age group (months, inclusive)	Relative risk of diarrhoea morbidity by feeding mode[a]		Episodes of diarrhoea per child per year, by breast-feeding pattern (Table 3)[c]			Proportion (%) of 0–59 month-old children falling within the stated age group
	Part BF vs Excl. BF[b]	No BF vs Excl. BF[b]	A	B	C	
0–2	2.0	4.0	1.0	2.0	3.0	7
3–5	2.0	4.0	1.0	2.0	3.0	6
6–11	1.3	1.6	1.5	3.0	4.0	11
12–59	1.0	1.0	0.5	1.5	2.0	76

[a] See Annex 1 and Fig. 1 and 2.

[b] For definitions of feeding modes, see footnote *b* to Annex 1.

[c] Estimates derived from Snyder & Merson (*74*).

depend on the assumptions made on age-specific morbidity and mortality rates in Tables 6 and 8 (see footnotes *b* to Tables 7 and 9). These rates are based on the assumption that breast-feeding pattern A will most commonly be found in relatively wealthy communities having relatively low diarrhoea rates, whereas pattern C will be typical of very poor communities having the highest diarrhoea rates. Communities with breast-feeding pattern B are assumed to have intermediate diarrhoea rates. This generalization does not reflect the situation in all countries. There are areas having low breast-feeding prevalence but high diarrhoea rates (for instance, in urban slums in some Latin American cities), and there are areas having high breast-feeding prevalences but low diarrhoea rates (for instance, in Sweden).

The former case, of low breast-feeding prevalence and high diarrhoea rates, is of particular interest. A community was defined having breast-feeding pattern A (Table 3), but with diarrhoea morbidity and mortality rates the same as those assumed for communities with breast-feeding pattern C (Tables 6 and 8). Such a community might be found in an urban slum in Latin America. The age-specific percentage reductions in diarrhoea morbidity and mortality rates due to breast-feeding promotion in this community are exactly as calculated in Tables 7 and 9 for a community with breast-feeding pattern A. This is because the age-specific morbidity and mortality rate reductions are not dependant on the assumed diarrhoea rates; they depend rather on the relative risks by feeding mode and it has been assumed throughout these computations that these relative risks are the same in communities having breast-feeding patterns A, B and C. The diarrhoea rate reductions for the total 0–59-months age group are

Table 7. Percentage reductions in diarrhoea morbidity rates, by age of child, due to breast-feeding promotions of varying effectiveness

Pre-intervention pattern of breast-feeding[a]	Age of children (months, inclusive)	Reduction (%) in diarrhoea incidence by effectiveness of breast-feeding promotion[b]		
		High impact[c]	Medium impact[c]	Low impact[c]
A	0–2	39	20	10
	3–5	34	17	8
	6–11	4	2	1
	12–59	0	0	0
	0–59	8	4	2
B	0–2	31	15	8
	3–5	29	14	8
	6–11	2	1	0
	12–59	0	0	0
	0–59	5	2	1
C	0–2	16	8	4
	3–5	21	9	6
	6–11	1	0	0
	12–59	0	0	0
	0–59	3	1	1

[a] See Table 3.

[b] For reductions in the 0–2, 3–5, 6–11, and 12–59 months age groups the given percentage reductions are applicable, whatever the incidence of diarrhoea or the age structure in the community. The percentage reductions in the 0–59 months age group are calculated using the assumptions on diarrhoea incidence and age structure given in Table 6.

[c] See Table 5.

dependent on the age-specific diarrhoea rates assumed. However, similar percentage reductions are computed for the urban community in Latin America as for the more typical pattern A community (Tables 7 and 9), because the higher diarrhoea rates apply not only to the first 6 months of life when changes in breast-feeding are effective, but also to the next 4.5 years when they are not.

Clearly the absolute, rather than the proportional, reduction in diarrhoea morbidity and mortality rates will be higher in communities having higher initial diarrhoea rates. For instance, a community having breast-feeding pattern A and diarrhoea rates for that pattern as shown in Table 6, will have 67 diarrhoea episodes per 100 children under 5 years old per year. Following a breast-feeding promotion of high impact, there will be 61.5 episodes per year, an 8% reduction (Table 7) with only 5.5 episodes averted annually per 100 children under 5 years old. The Latin American slum community characterized above (breast-feeding pattern A, but diarrhoea rates as assumed for communities with pattern C), will have initially 233 episodes of diarrhoea per 100 children under 5 years old per year. Following a breast-feeding promotion of high impact, there will be 216 episodes per year, only a 7% reduction but with 17 episodes per year averted. Precisely the same arguments hold for mortality reductions.

A final note of caution is necessary. The impacts computed in Tables 7 and 9 depend on median relative risk data drawn from Annexes 1 and 2 and summarized in Fig. 1–4. In the relative risks of morbidity (Fig. 1 and 2) one may have considerable confidence. The studies are numerous, some are recent and some have used sophisticated epidemiological methods. In the relative risks of mortality one must have much less

Table 8. Assumptions made in calculating the impact of breast-feeding promotions on diarrhoea mortality

Age group (months, inclusive)	Relative risk of diarrhoea mortality, by feeding mode[a]		Diarrhoea deaths per 1000 children per year, by breast-feeding pattern (Table 3)[c]			Proportion (%) of 0–59 month-old children falling within the stated age group
	Part BF vs Excl. BF[b]	No BF vs Excl. BF[b]	A	B	C	
0–5	8.0	25.0	11	24	40	13
6–11	1.0[d]	1.0[d]	9	16	20	11
12–59	1.0	1.0	3	6	12	76

[a] See Annex 2 and Fig. 3 and 4.

[b] For definitions of feeding modes, see footnote *b* to Annex 1.

[c] Estimates derived from Puffer & Serrano (*67*) and Snyder & Merson (*74*).

[d] It is possible that the relative risk in this age group is > 1, but there is inadequate data on which to estimate a value and so a conservative value of 1 has been adopted.

Table 9. Percentage reductions in diarrhoea mortality rates, by age of child, due to breast-feeding promotions of varying effectiveness

Pre-intervention pattern of breast-feeding[a]	Age of children (months, inclusive)	Reduction (%) in diarrhoea mortality rate by effectiveness of breast-feeding promotion[b]		
		High impact[c]	Medium impact[c]	Low impact[c]
A	0–5	56	26	13
	6–11[c]	0	0	0
	12–59	0	0	0
	0–59	17	8	4
B	0–5	54	27	16
	6–11[d]	0	0	0
	12–59	0	0	0
	0–59	18	9	5
C	0–5	44	24	14
	6–11[d]	0	0	0
	12–59	0	0	0
	0–59	14	8	4

[a] See Table 3.

[b] For reductions in the 0–5, 6–11, and 12–59 months age groups the given percentage reductions are applicable, whatever the diarrhoea mortality rates or the age structure in the community. The percentage reductions in the 0–59 months age group are calculated using the assumptions on diarrhoea mortality rates and age structure given in Table 8.

[c] See Table 5.

[d] See comment in footnote *d* to Table 8.

confidence for the reasons discussed above. Modern studies are needed on diarrhoea mortality by feeding mode to confirm or deny the substantial mortality reductions predicted in Table 9.

A recent study in Costa Rica (*56*) has documented a dramatic impact of breast-feeding promotion on neonatal diarrhoea morbidity and mortality. Between 1976 and 1980 hospital routines were changed so as to promote early breast-feeding and close mother-child contact. Over the same period neonatal diarrhoea morbidity fell by 91% from 17.7 to 1.6 cases per 1000 live births, and neonatal diarrhoea mortality fell from 3.9 to 0 deaths per 10 000 live births. These changes were attributed mainly to the emphasis given to the ingestion of colostrum by neonates. Another report of the same study (*57*) showed that the incidence of diarrhoea among infants aged 0–5 months was 36% lower in a population receiving intense breast-feeding promotion (only 15% of infants aged 5 months receiving no breast milk) than in a population receiving less intense promotion (41% of infants aged 5 months receiving no breast milk).

These morbidity reduction data from Costa Rica (*57*) agree closely with the theoretical calculations described above. The level of breast-feeding promotion in this population (where the prevalences of non-breast-fed infants were 10–19% at 0–2 months, 27–41% at 3–5 months, and 63% at 9 months) stands mid-way between breast-feeding patterns A and B in Table 3. It is predicted in Table 5 that a breast-feeding promotion of high impact would reduce these prevalences to 2–4% at 0–2 months, 10–16% at 3–5 months, and 50% at 9 months. The actual prevalences of non-breast-fed infants in the population where there was intense promotion in Costa Rica were 5–11% at 0–2 months, 13–16% at 3–5 months, and 31% at 9 months. The reduction in diarrhoea morbidity among infants aged 0–5 months, caused by a high-impact breast-feeding promotion, is predicted to be 34–39% in communities having breast-feeding pattern A, and 29–31% in communities having pattern B (Table 7). The actual reduction in morbidity among children aged 0–5 months in Costa Rica was reported to be 36%. This agreement between theoretical calculations and the Costa Rican experience suggests that the morbidity and mortality reductions predicted in Tables 7 and 9 may be achievable in practice, especially the more modest reductions predicted for a breast-feeding promotion with only medium impact.

FEASIBILITY AND COSTS

The promotion of breast-feeding, which has been reviewed elsewhere (*39*, *51*, *85*),[f] is generally of two kinds: information and support programmes and changes in hospital routine. The most cost-effective designs for these interventions in various societies are not known. Changes in hospital routine have to be made only once and they may not involve any increase in operating costs. However, such interventions will be effective only in societies where a substantial proportion of deliveries take place in hospitals where they are more likely to affect the initiation of breast-feeding than its duration. It is likely that a combination of information and support programmes, together with changes in hospital routine, will prove to be the most cost-effective intervention in many societies.

Costs of breast-feeding promotion activities have not been documented but they are probably low in comparison with most other anti-diarrhoea interventions. Studies of both the financial and the economic costs of breast-feeding compared to bottle-feeding have shown that breast-feeding is the cheaper alternative (*51*, *52*).

[f] See footnote *c* on page 272.

CONCLUSIONS

The literature on breast-feeding and diarrhoea is of varied quality; sometimes the findings are contradictory and substantial areas of ignorance remain. The purpose of this review is to attempt to draw a consensus from the literature.

Breast-feeding, whether exclusive or partial, appears to offer protection to children up to one year of age, but not beyond (Fig. 1 and 4). Protection is greatest in the first 3 months of life and falls thereafter (Fig. 1 and 3). During the first half year of life, exclusive breast-feeding is more protective than partial breast-feeding and partial breast-feeding is protective compared to no breast-feeding (Fig. 2 and 4).

The data summarized in Fig. 2 and 4 are suggestive of the possible mechanisms of protection of breast-feeding. If protection were due solely to the immunological and antimicrobial properties of the breast milk itself, then the relative risk of no breast-feeding versus partial breast-feeding might approximate that of no breast-feeding versus exclusive breast-feeding. In fact these relative risks are substantially different (Fig. 2 and 4). If protection were due solely to the contamination of foods other than breast milk, then the relative risk of no breast-feeding versus exclusive breast-feeding might approximate that of partial breast-feeding versus exclusive breast-feeding. This would also be the case if protection was caused solely by the dominant colonization of the intestine by *Bifidobacterium* (a feature only of exclusively breast-fed infants). In fact these relative risks are substantially different (Fig. 2 and 4). Thus the relative risks computed suggest that the protection is caused neither by breast-milk properties alone, nor by the "bifid" factor alone, nor by food contamination alone, nor by a combination of the last two mechanisms alone. Some combination of these three mechanisms, together with the non-specific nutritional benefits of breast-feeding, may be responsible for the observed degree of protection. The evidence that protection is not caused by food contamination alone is further supported by the protective effect of breast-feeding for infants in families of high socioeconomic status in developed countries, such as Canada, England, Finland, New Zealand and the USA (Annex 1). It is probable that the mechanisms of protection, and their relative importance, vary by pathogen and by the age of the infant.

The literature on breast-feeding promotion shows that breast-feeding may become substantially more common following changes in hospital routine combined with information and support programmes for mothers. Theoretical calculations show that a typical breast-feeding promotion may reduce diarrhoea mortality by 24–27% among infants aged 0–5 months and by 8–9% among children under 5 years of age (Table 9).

Only one study on the actual impact on diarrhoea of breast-feeding promotion has been located (*56*, *57*). This study, from Costa Rica, found substantial reductions in neonatal diarrhoea morbidity and mortality and a 36% reduction in diarrhoea morbidity among infants aged 0–5 months. A detailed comparison between the Costa Rican data and the theoretical calculations presented in this paper shows good agreement and gives confidence that the predicted morbidity and mortality reductions set out in Tables 7 and 9 can be achieved in practice.

This review has highlighted several areas of ignorance that require further research. The highest research priority is to determine the level of protection against diarrhoea mortality afforded by partial or exclusive breast-feeding among infants in various socioeconomic settings in developing countries. Well designed studies of diarrhoea morbidity by feeding mode in developing countries are also urgently needed. Studies are required into the relationships between diarrhoea severity and feeding mode and into the possible lack of association between the relative risk of diarrhoea in non-breast-fed infants and the socioeconomic status of their families. The relationships between breast-feeding and chronic diarrhoea, and the protection against nosocomial diarrhoea that may be afforded by the continued breast-feeding of hospitalized infants, are worthy of investigation.

All these studies should be etiology-specific in order to clarify the undoubted differences in the levels of protection provided by breast-feeding against diarrhoeas of different etiology. The design of these studies requires careful and detailed planning. Fine age ranges must be used and several important confounding variables must be controlled. These requirements will tend to lead to study designs having many cells and large overall sample sizes. A prospective study may often be unduly expensive and complicated and a case-control approach will be preferable in these situations.

As regards operational research, more information is needed on the design, effectiveness, and cost of breast-feeding promotion in developing countries. Where possible, effectiveness should be measured not only by impact on breast-feeding patterns but also by impact on diarrhoea rates. This latter kind of impact measurement will typically require major prospective studies, like that reported from Costa Rica. For these studies to be worthwhile they must be very carefully designed and must incorporate a detailed analysis of the financial and economic costs of the breast-feeding promotion.

Despite the limitations in the mortality data, and the need for continued research as discussed above,

the evidence that breast-feeding protects young infants from diarrhoea is strong. Governmental and other agencies with responsibility for diarrhoea control should act to promote breast-feeding on the basis of the evidence now available. Research will generate new understandings, both fundamental and operational, which will improve the effectiveness of these breast-feeding promotions.

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RÉSUMÉ

INTERVENTIONS POUR LA LUTTE CONTRE LES MALADIES DIARRHEIQUES CHEZ LE JEUNE ENFANT: ENCOURAGEMENT DE L'ALLAITEMENT MATERNEL

Le présent article est le troisième d'une série d'études sur ce qu'on peut faire dans les pays en développement pour abaisser la morbidité et la mortalité dues à la diarrhée chez l'enfant de moins de cinq ans. Il existe une documentation très fournie sur les risques relatifs de morbidité enfantine selon les différents modes d'alimentation. Cette documentation souffre de plusieurs problèmes méthodologiques. On a examiné 35 études émanant de 14 pays. Quatre-vingt-trois pour cent de ces études constatent que l'allaitement maternel total est plus protecteur que l'allaitement maternel partiel, 88% des études constatent que l'allaitement maternel total est plus protecteur que l'absence d'allaitement maternel et 76% constatent que l'allaitement maternel partiel est plus protecteur que l'absence d'allaitement maternel. Si l'on compare les enfants que ne reçoivent pas de lait maternel avec ceux qui sont nourris au sein totalement ou partiellement, le risque médian relatif est de 3 entre 0 et 2 mois, de 2,4 entre 3 et 5 mois et de 1,3 à 1,5 entre 6 et 11 mois. Au-delà d'un an d'âge, il n'y a pas d'effet protecteur visible de l'allaitement maternel contre la morbidité diarrhéique. Si l'on compare les enfants qui ne reçoivent pas de lait maternel avec ceux qui sont nourris entièrement au sein, le risque médian relatif est de 3,5 à 4,9 dans les six premiers mois de la vie. D'après la documentation étudiée, rien n'indique que le risque relatif de morbidité pour les enfants nourris au biberon soit plus élevé dans les familles pauvres que dans les familles plus riches. Par ailleurs, l'effet protecteur de l'allaitement maternel ne semble pas subsister après la cessation de cet allaitement. Par contre, il y a des signes d'augmentation considérable de la gravité de la maladie chez l'enfant nourri au biberon.

Il existe peu d'ouvrages, et ils sont pour la plupart antérieurs à 1950, sur les risques relatifs de mortalité du nourrisson selon le mode d'alimentation. On a examiné neuf études émanant de cinq pays, et la plupart montrent que l'allaitement maternel est une protection substantielle contre le risque de mortalité. Si l'on compare les nourrissons qui ne reçoivent pas de lait maternel avec ceux qui sont nourris uniquement au sein, le risque médian relatif de décès est de 25 dans les six premiers mois de la vie. Si l'on compare des enfants nourris totalement au sein et des enfants nourris partiellement au sein, le risque tombe à 8,6.

On peut encourager l'allaitement maternel en changeant les habitudes hospitalières, ainsi qu'en éduquant et en aidant les mères. L'examen de 21 études émanant de 8 pays montre que selon toute probabilité on peut ainsi abaisser la prévalence de la maladie chez les sujets ne recevant pas de lait maternel de 40% entre 0 et 2 mois, de 30% entre 3 et 5 mois et de 10% entre 6 mois et un an. Des calculs théoriques fondés sur ces chiffres montrent qu'une action d'envergure moyenne d'encouragement de l'allaitement maternel peut faire diminuer la morbidité diarrhéique dans une proportion de 8% à 20% et la mortalité dans une proportion de 24% à 27% au cours des six premiers mois de la vie. Pour les enfants âgés de 0 à 59 mois, la morbidité serait réduite dans une proportion de 1% à 4% et la mortalité dans une proportion de 8% à 9%. Une étude récente faite au Costa Rica a démontré une incidence substantielle de l'encouragement de l'allaitement maternel sur la morbidité et la mortalité du nouveau-né, et sur la morbidité du nourrisson de 0 à 5 mois. Les données costa-riciennes concordent avec les calculs théoriques présentés ici.

Plusieurs aspects importants de l'allaitement maternel et des maladies diarrhéiques doivent encore être éclairés par la recherche. Toutefois, la nécessité de cette recherche ne doit pas retarder l'action en vue d'encourager l'allaitement maternel et d'en surveiller les effets sur les pratiques alimentaires et sur la diarrhée.

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Annex 1

Relative risk of diarrhoea morbidity by feeding mode

Country/place	Date of study	Socio-economic status	Age group (inclusive)	Relative risk of diarrhoea morbidity[a]			Factors controlled	Reference
				Part BF vs Excl. BF[b]	No BF vs Excl. BF[b]	No BF vs Part BF[b]		
Bahrain[c]	1978	?	0–11 mo.			7.0	Case-control study. Pairs matched for age and place of residence (rural/urban). Water-related habits and child care practices were not risk factors for cholera.	*37*
Canada								
Toronto	1939	?	0–11 mo.			5.80		*13*
Manitoba Indian reservation	1972–75	Lower	0–11 mo.		10.32		Marital status of mother, occupation of father, and family income were not associated with breast-feeding. Women who breast-fed for > 12 mo. were older, had more children, less education, and lived in more crowded houses than those who breast-fed for < 12 mo.	*15*
Urban	?	?	0–23 mo.			3.20	Feeding modality controlled for socioeconomic status, parental education, and family size.	*5*
Winnipeg[d]	1976–79	All	0–16 mo.			1.41		*38*
Colombia	1964–65	Lower	0–5 mo. 6–11 mo.	2.37 2.37	2.91 1.64	1.33 0.69		*88*
Costa Rica	1979–82	Lower	0–2 mo. 3–5 mo. 6–8 mo. 9–11 mo.	1.37 3.31	6.47 6.92	4.73 2.09 1.29 1.00		*59*
England								
Liverpoool	1936	Lower/ middle	3–26 wk	6.36	12.85	2.02		*69*
Nationwide	1946–48	Lower	0–3 mo. 4–8 mo. 9–23 mo.	2.57	3.20	1.24 0.79 0.91		*12*
Oxford	?	?	2–11 mo.	2.98	2.33	0.78		*76*

South-east	1968–69	Upper/ middle	0–11 mo.			3.89	Sex, date of birth, birth weight, ages of parents, number of persons per house, number of sibs, and number of sibs at school, were not associated with breast-feeding.	*68*
Nationwide	1970–75	All	0–11 mo.			1.55	Feeding modality controlled for maternal age, child's sex, birth weight, birth rank, maternal smoking, and socio-economic status.	*78*
Ethiopia								
Addis Ababa	1979	All	0–5 mo.	6.19	9.14	1.48		*80*
			6–11 mo.	0.34	0.67	1.99		
Finland								
4 towns	1949	?	0–11 mo.		3.04			*89*
Guatemala	1964	Lower	3–5 mo.	0.85				*32*
			6–8 mo.	1.14				
			9–11 mo.	1.32				
India								
Punjab	1955–59	Lower	0–2 mo.	1.26				*31*
			3–5 mo.	1.39				
			6–8 mo.	1.17				
			9–11 mo.	1.55				
New Delhi								
rural	?	Lower	3–5 mo.	1.39				*27*
			6–8 mo.	1.02				
			9–11 mo.	0.95				
urban	?	Middle	3–5 mo.	1.14				
			6–8 mo.	0.97				
Rural	?	?	0–11 mo.			3.01	Feeding modality controlled for socioeconomic status, parental education, occupation, and family size.	*5*
New Delhi	?	Lower	0–5 mo.		5.53		Cases and controls were socio-economically matched and both groups were hospitalized.	*61*
			6–11 mo.		1.20			
Israel	1971	Lower	0–5 mo.	10.47			Twins and infants with low birth-weight or birth defects were excluded.	*46*
Jamaica	1967–68	?	0–3 mo.		3.39[c]		Lower socioeconomic status, non-working mothers at 6 mo. post-birth, and no cribs, were associated with breast-feeding.	*34*

New Zealand								
Christchurch	1977	Upper/ middle	(treated diarrhoea)				Relative risks remained significant when controlled for maternal age, parity, parental education, race, number of parents, living standard, gestation period, and birth weight.	*22*
			0–3 mo.	2.41	3.60	1.49		
			(all diarrhoea)					
			0–3 mo.	3.92	4.99	1.27		
Christchurch	1977–79	Upper/ middle	(treated diarrhoea)				Relative risks for 0–3 mo. group remained significant when controlled for child's sex, maternal age, race, education, smoking, family size, number of parents, and quality of child care.	*23*
			0–3 mo.			2.06		
			4–11 mo.			1.23		
			12–23 mo.			0.88		
			(all diarrhoea)					
			0–3 mo.			2.81		
			4–11 mo.			1.21		
			12–23 mo.			0.97		
Uganda								
Villages near Kampala	1955	All	0–5 mo.	1.71				*82*
			6–11 mo.	0.64				
USA								
Chicago	1924–29	Lower	2 wk–8 mo.			1.83		*35*
Chicago	1924–29	Lower	0 mo.	2.24	0.95	0.42		*36*
			1 mo.	3.00	0.23	0.08		
			2 mo.	3.71	1.90	0.51		
			3 mo.	2.55	2.01	0.79		
			4 mo.			1.67		
			5 mo.			2.29		
			6 mo.			2.63		
			7 mo.			2.72		
			8 mo.			4.34		
Boston	1930–40	All	0–11 mo.			1.20		*75*
Navajo Indian reservation	1960	Lower	0–2 mo.		4.20[c]			*25*
			3–5 mo.		2.78[c]			
			6–8 mo.		1.38[c]			
			9–11 mo.		1.98[c]			
California	1973–75	Upper/ middle	0–2 mo.			5.77		*49*
Iowa	1973–78	Upper/ middle	0–5 mo.			4.15	Number of parents, number of sibs, number of clinic visits of infants with no sibs and those with one or more, parental education, urban vs rural, were not significantly associated with breast-feeding.	*63*

Cooperstown, NY	1974	Upper/ middle	0–11 mo.		1.97	Relative risks (of all illnesses) remained significant when parental education, maternal age, family size, birth weight, sex, Apgar score, and birth month were controlled. Higher relative risks (of all illnesses) were associated with male infant, lower maternal age, larger family size, and lower birth-weight.	*7, 8, 9*
Arkansas[f]	1977–78	Upper/ middle	0–11 mo.		96.0		*24*
Syracuse	1978	?	0–3 mo.	2.70			*18*
New York City	?	Lower	0–5 mo.		2.72	Feeding modality was controlled for mother's age, parity, ethnicity, and education.	Footnote *g*
Albuquerque, New Mexico	1979	All	0–11 mo.		2.01	Breast-feeding was associated with maternal age and education, home-ownership, and ethnicity, but not with sex, maternal career, family size, water source, medical care source, or day care.	*10*

[a] The relative risk of feeding mode X compared to feeding mode Y is computed by dividing the incidence of diarrhoea for children on feeding mode X by that for children on feeding mode Y. When incidence data were not reported, prevalence was used or the relative risk was computed from data on the distribution of feeding modes among infants with diarrhoea compared to healthy infants.

[b] Categories of feeding mode are defined as follows: Excl. BF = children receiving only breast milk throughout the stated age range; Part BF = children receiving breast milk and other milk and/or food throughout the stated age range and children receiving only breast milk or breast milk plus other milk/food for part of the stated age range; No BF = children receiving no breast milk throughout the stated age range.

[c] This study relates to cholera diarrhoea only.

[d] This study relates to rotavirus diarrhoea only.

[e] Children described as No BF included some who were Part BF and some who were No BF, but these two groups could not be separated.

[f] This study relates to *Salmonella* diarrhoea only.

[g] SOLIMANO, G. ET AL. Morbidity patterns in breast-fed and non-breast-fed infants in a low socioeconomic urban U.S. population. Poster session. *12th International Congress of Nutrition, San Diego, CA, 1981.*

Annex 2

Relative risk of diarrhoea mortality by feeding mode[a]

Country/place	Date of study	Socio-economic status	Age group (inclusive)	Relative risk of diarrhoea mortality[b]			Factors controlled	Reference
				Part BF vs Excl. BF[c]	No BF vs Excl. BF[c]	No BF vs Part BF[c]		

Canada Toronto	1939	?	0–11 mo.			6.48		*13*
Egypt Menoufia	1979–80	Lower	0–11 mo.	3.33[d]				*79*
England Derby[e]	1900–03	Lower	0–11 mo.	2.53	5.83	2.31	Children born prematurely, or with defects or malformations, were excluded. Better housing associated with bottle-feeding.	*44*
Liverpool	1884–86	?	0–2 mo.		15			*62*
Finsbury[e]	1901–04	?	0–2 mo. 6–8 mo.	9.82	25.24 10.99	2.57		*62*
Brighton	1903–05	?	0–2 mo. 3–5 mo.	7.33	29.15 43.24	3.98		*62*
Croydon	1904	?	0–5 mo.		17.22			*62*
Liverpool	1936–42	Lower/ middle	3–26 wk	3/0[f]	6/0[f]	3.50	Premature and 'weakly' children were excluded.	*69*
Sweden Stockholm	1943–47	All	1–11 mo. 2–11 mo.	1.08 3.25	6.79 18.75	6.27 5.77	Breast-feeding associated with better child care. Relative risks (of total mortality) not influenced by age of mother or birth-weight.	*54*
USA Boston[e]	1911	All	2 wk–11 mo.			13.02		*11*
8 cities[e]	?	All	1–8 mo. 9–11 mo. 0–11 mo.		11.3 3.5 7.71		Relative risks (of total mortality) remained substantial when race, nationality, prematurity, maternal death, and plural birth were controlled. Relative risks (of total mortality) was higher in lower income groups.	*87*
Chicago	1924–29	Lower	2 wk–8 mo.			18.82		*35, 36*

[a] All the studies summarized here contain severe methodological flaws and the relative risks derived should be regarded as indicative only.

[b] The relative risk of feeding mode X compared to feeding mode Y is computed by dividing the diarrhoea mortality rate of children on feeding mode X by that for children on feeding mode Y. Where mortality rates were not reported, the relative risk was computed from data on the distribution of feeding modes among infants who died from diarrhoea compared to healthy infants.

[c] For definitions of feeding modes see footnote *b* to Annex 1.

[d] To compute this relative risk it was necessary to assume that the distribution of feeding modes among infants who died from causes other than diarrhoea was identical to that of infants in the general population. Provided that breast-feeding is not a risk factor for non-diarrhoea deaths, this assumption can only lead to an underestimation of the relative risk.

[e] Rates based on over 100 diarrhoea deaths.

[f] There were 0 deaths in the Excl. BF group.

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Interventions for the control of diarrhoeal diseases among young children: prevention of low birth weight*

ANN ASHWORTH[1] & R. G. FEACHEM[2]

The effect of low birth weight (LBW) on diarrhoea morbidity and mortality is analysed and interventions to increase birth weights are reviewed. Birth weight is a major determinant of infant mortality and, in developed countries at least, its effect on neonatal mortality is independent of socioeconomic status. We have located no satisfactory data on LBW as a determinant of diarrhoea mortality or morbidity. The strong association between LBW and mortality, however, makes it likely that there is an association between LBW and diarrhoea mortality in developing countries where diarrhoea is a major cause of infant death. Poor maternal nutrition, certain infections, pre-eclampsia, arduous work after mid-pregnancy, short birth intervals, and teenage pregnancy are likely to be causally associated with LBW in developing countries. Tobacco and alcohol consumption are additional risk factors.

Of the interventions examined, maternal food supplementation has been the most studied. If targeted to mothers at nutritional risk, and if the food is consumed in addition to the usual diet, the prevalence of LBW can be expected to be reduced. However, food supplementation can be expensive and the results from carefully supervised feeding trials may be better than those that can be achieved in national programmes. The effect of supplementation with iron, zinc or folate requires further study. If it were possible to intervene in maternal nutrition, health and life-style in a developing country in a way that reduced the prevalence of LBW from around 30% to around 15%, a fall in the infant mortality rate of around 26% would be expected. The fall in infant diarrhoea mortality rate might be similar. The scarce data on relative risk of morbidity by birth weight do not allow any comparable computations for morbidity reductions to be made.

This review confirms that whatever its association with diarrhoea, LBW is an important determinant of infant mortality. For the more general goal of reducing infant mortality it is necessary to know more about the nature, etiology, and prevention of LBW in developing countries.

In this review, the effect of low birth weight on diarrhoea morbidity and mortality is analysed and interventions to increase birth weight are reviewed. While recognizing that the etiology of low birth weight is multifactorial, emphasis is given to those maternal factors that are believed to be of greatest importance in developing countries and that may be amenable to change in the short term. These include inadequate dietary intake, infections, arduous workloads, teenage pregnancy, short birth intervals, and excessive tobacco or alcohol consumption. This paper examines whether interventions that reduce the prevalence of low birth weight might be effective in reducing morbidity or mortality from diarrhoeal diseases among young children. This review is the fifth in a series of reviews of potential anti-diarrhoea interventions being published in the *Bulletin of the World Health Organization* (*33–37*).

* Requests for reprints should be sent to the Director, Diarrhoeal Diseases Control Programme, World Health Organization, 1211 Geneva 27, Switzerland.

[1] Lecturer, Department of Human Nutrition, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, England.

[2] Reader in Tropical Public Health Engineering and Head of Department of Tropical Hygiene, London School of Hygiene and Tropical Medicine, London, England.

EFFECTIVENESS

If the prevention of low birth weight, by improving the nutritional status, health or life-style of pregnant women, is to be an effective diarrhoea control

Table 1. Percentage distribution of live births by birth weight in four countries

	Percentage of live births														
												India			Guatemala
Birth weight (g)	Oregon (Portland)	USA (5 regions)	USA (white)	California	USA	New York (white)	New York	USA (non-white)	Brazil (Recife)	Colorado (Denver)	New York (black)	New Delhi	North Arcot	Palghar	(Santa Maria Cauqué)
< 1501	0.8	0.8	1.0	1.0	1.2	0.9	1.6	2.2	1.7	3.9	3.0	2.8	1.1	5.2	1.2
1501–2000	0.9	1.1	1.3	1.5	1.4	1.3	1.8	2.5	2.8	3.4	3.0		5.5	9.4	6.5
2001–2500	3.5	4.2	4.5	5.1	5.1	5.7	6.6	8.3	10.0	8.0	9.8	20.2	25.3	23.2	34.0
2501–3000	15.6	17.8	17.2	19.1	18.5	22.7	23.9	25.3	33.0	24.9	28.4	45.8	41.2	37.4	48.1
3001–3500	38.1	39.2	38.1	39.5	38.0	40.6	39.6	37.1	35.0	36.9	36.6	25.8	21.5	22.4	10.0
3501–4000	30.4	27.7	28.2	26.0	26.8	22.6	21.0	18.9	14.8	18.4	15.8	4.8	4.8	2.4	0.2
> 4000	10.6	9.1	9.6	7.8	9.0	6.2	5.5	5.8	2.6	4.5	3.5	0.6	0.7	0.0	
% LBW	5.2	6.1	6.8	7.6	7.8	8.0	10.0	12.9	14.5	15.2	15.7	23.0	31.9	37.8	41.7
Reference	*10*	*110*	*20*	*91*	*20*	*21*	*21*	*20*	*82*	*55*	*21*	*91*	*93*	*103*	*70*

intervention, it must be true that:

either

a considerable proportion of diarrhoea morbidity or mortality in young children in developing countries is due to low birth weight	*hypothesis 1*

and

improving the nutritional status, health or life-style of pregnant women can reduce the prevalence of low birth weight	*hypothesis 2*

or

improving the nutritional status, health or life-style of pregnant women can reduce diarrhoea morbidity or mortality rates in young children	*hypothesis 3*

The literature on hypothesis 2 is extensive, whereas hypotheses 1 and 3 have been little studied. The effectiveness of low-birth-weight prevention as an intervention to reduce diarrhoea morbidity or mortality would be suggested by a demonstration either of the correctness of hypotheses 1 and 2 or of the correctness of hypothesis 3. The evidence for and against these hypotheses is examined below.

Hypothesis 1. *A considerable proportion of diarrhoea morbidity or mortality in young children in developing countries is due to low birth weight.*

Prevalence and distribution of low birth weight. The term low birth weight (LBW) is used to describe infants who weigh less than 2500 g at birth. From sample surveys and country reports, WHO has estimated that over 20 million LBW infants are born each year. At the global level this represents 16% of all births, but the proportion is not uniform and national rates range from 4% in Scandinavia to around 50% in parts of India and Bangladesh (*124*, *125*). Table 1 compares birth weight distributions in 15 populations with different LBW prevalence rates, ranging from 5% to 42%.

Infants with a low birth weight may be divided into two broad subgroups: (*a*) those who are born preterm, that is of less than 37 weeks' gestation; (*b*) those who are growth-retarded *in utero* and are born small for gestational age (SGA). Investigators are not consistent in their definition of SGA, but it may be defined as a birth weight of 2SD or more below the mean birth weight for gestational age. Although most preterm infants are appropriate for gestational age (AGA), some LBW infants are both preterm and SGA. In the developed countries the majority of LBW infants are the result of a preterm delivery. In contrast, in developing countries it would seem from the limited information available that the majority of LBW infants are small for gestational age. For example, in 18 reports from the Indian subcontinent, south-east Asia and Latin America, between 65% and 96% of LBW infants were small for gestational age (*124*). In Africa, there are data for only 5 cities and these show a more diverse pattern with between 34%

Table 2. Association of low birth weight and infant mortality in developing countries

Region or country	Place	Prevalence of LBW (%)	Percentage of deaths weighing < 2500 g at birth			Reference
			Neonatal	Post-neonatal	Infant	
Latin America and Caribbean		—[a]	—	—	47	*89*
Nigeria	Igbo-Ora	11	—	—	42	*4*
India	Hyderabad	21	84	—	—	*80*
India	North Arcot	32	56	42	48	*93*
Guatemala	Santa Maria Cauqué	42	87	58	70	*69*

[a] — denotes data not available.

Table 3. Relative risks of neonatal mortality by birth weight compared to birth weight of 2501–3000 g

	Relative risk of neonatal mortality												
Birth weight (g)	California (1977)	USA (5 regions (1974–75)	Norway (1967–78)	California (1969–70)	Oregon (Portland) (1959–66)	USA (white) (1960)	Colorado (Denver) (1974–80)	USA (1960)	India (Delhi) (1969–72)	USA (non-white) (1960)	Brazil (Ribeirao Preto) (1968–70)	India (N. Arcot) (1969–75)	Guatemala (Santa Maria Cauqué) (1964–72)
1001–1500	52.7	99.9[a]	41.1	80.5	47.5	55.0	32.8	52.6	94.2	46.2	41.4	16.7[a]	
1501–2000	13.5	17.6	16.6	19.8	20.6	19.6	9.4	18.2	30.8	13.9	23.3	4.4	27.3
2001–2500	3.0	3.8	4.5	5.2	4.4	4.4	2.1	4.2	4.5	3.3	4.0	1.4	3.4
2501–3000	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
3001–3500	0.3	0.5	0.4	0.5	0.4	0.4	0.3	0.5	1.1	0.7	0.5	0.8	
3501–4000	0.3	0.3	0.2	0.4	0.3	0.3	0.3	0.4		0.7	0.4	0.6	
4001–4500	0.3	0.4	0.2	0.6	0.2	0.4		0.4		1.1	0.5	1.4	
> 4500	0.4		0.3		0.3	0.8		0.9		1.7			
Neonatal mortality rate[b]	5.6	8.2	8.5	12.7	13.8	16.9	17.5	18.4	21.2	26.7	28.2	34.8	39.0
% LBW	unstated	6.1	5.2	unstated	5.2	6.8	15.2	7.8	23.2	12.9	8.7	31.9	41.7
No. of births	290 000	234 000	700 000	44 700	40 000	3.6 million	14 400	4.26 million	4 590	657 100	18 200	4 220	416
Reference	*123*	*110*	*30*	*90*	*10*	*20*	*55*	*20*	*41*	*20*	*90*	*93*	*69*

[a] Includes all births < 1500 g.

[b] Deaths per 1000 live births, except for ref. *123* (per 1000 single vaginal births), ref. *30* (per 1000 total births), and ref. *10* (per 1000 single, white, live births).

Table 4. Relative risks of post-neonatal mortality by birth weight compared to birth weight of 2501–3000 g

	Relative risk of post-neonatal mortality							
Birth weight (g)	Norway (1967–68)	USA (5 regions) (1974–75)	USA (white) (1960)	USA (1960)	USA (non-white) (1960)	India (Delhi) (1969–72)	India (N. Arcot) (1969–75)	Guatemala (Santa Maria Cauqué) (1964–72)
1001–1500	2.6	12.2[a]	6.3	6.1	4.8	9.3	4.5[a]	
1501–2000	3.0	3.7	3.5	3.4	3.0	5.3	2.3	7.0
2001–2500	1.8	1.9	1.9	1.9	1.8	2.2	1.1	0.8
2501–3000	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
3001–3500	0.6	0.6	0.6	0.6	0.7		0.6	0.5
3501–4000	0.5	0.5	0.5	0.5	0.7	0.7	0.4	
4001–4500	0.4	0.5	0.5	0.4	0.7			
> 4500	0.5		0.5	0.5	0.7			
Post-neonatal mortality rate[b]	3.2	4.3	5.4	6.9	15.1	25.3	51.6	60.0
% LBW	5.2	6.1	6.8	7.8	12.9	23.2	31.9	41.7
No. of births	700 000	234 000	3.6 million	4.26 million	657 100	4 590	4 220	416
Reference	*30*	*110*	*20*	*20*	*20*	*41*	*93*	*69*

[a] Includes all births < 1500 g.
[b] Deaths per 1000 survivors, except for ref. *30* (per 1000 total births) and ref. *110* (per 1000 live births).

and 73% of LBW infants being small for gestational age. More research is required to determine the relative proportion of these two subgroups of LBW infants in developing countries.

Association of low birth weight with mortality. In developed countries, LBW infants comprise the majority of infant deaths. For example, in a recent report from the USA, although LBW infants represented only 6% of live births they comprised 55% of infant deaths (*110*). Data from developing countries are limited since death registration is frequently incomplete and birth weights are rarely recorded. Indications are, however, that LBW infants similarly comprise a large proportion of infant deaths as shown in Table 2.

Birth weight has a marked association with neonatal mortality rates in both developed and developing countries. The relative risks of neonatal death among infants of different birth weights, compared with infants weighing 2501–3000 g, are shown in Table 3. The most favourable birth weights were in the range of 3500–4500 g. Although there were 7-fold differences in overall neonatal mortality rates among the 13 studies, the relative risks in each 500-g birth-weight interval were similar, except for Denver and North Arcot, where infants with birth weights of < 2500 g had lower relative risks than in the other places studied.

The association between birth weight and mortality extends into the post-neonatal period and birth weights of 3500–4500 g were similarly associated with the lowest risk. Table 4 shows that among LBW infants the relative risk of post-neonatal death in North Arcot was somewhat lower than that observed in developed countries, whereas in Delhi the relative risk among LBW infants was higher than in developed countries. In Santa Maria Cauqué, the relative risks were somewhat anomalous, perhaps because of the small number of subjects in this study.

It is possible that there is also an association between birth weight and mortality in the 1–4-year age group. In the Gambia, child mortality is significantly higher in children born in the wet season (when the incidence of LBW is high) than in children born in the dry season (*85*), and there is some indication from Guatemala that SGA infants may have an increased 1–4-year mortality risk (*68*, *71*). In view of the limited data available, however, it has been conservatively assumed in the calculations which follow that low birth weight confers no increased risk of death beyond the first year of life.

In populations where the whole Gaussian distribution of birth weights is shifted to the left, leading to a lower mean birth weight, it is possible that the definition of LBW based on a cut-off point of 2500 g is

Table 5. Neonatal and post-neonatal mortality rates by birth weight and gestational age

Birth weight (g)	Gestational age	Mortality rate			
		Santa Maria Cauqué	Delhi	North Arcot	New York City
		Neonatal mortality rate (deaths per 1000 live births)			
< 2500	Preterm	323	87	73	93
	Term (SGA)	28	27	41	44
> 2500	Preterm	—[a]	10	30	—[b]
	Term	8	4	21	—[b]
		Post-neonatal mortality rate (deaths per 1000 survivors)			
< 2500	Preterm	286	46	66	16
	Term (SGA)	58	35	66	13
> 2500	Preterm	—[a]	18	50	—[b]
	Term	42	13	42	—[b]
Reference		*69*	*41*	*93*	*117*

[a] No infants in this category.
[b] No data available.

too rigid (*95*). In such populations the relative risk of neonatal or post-neonatal death among births of < 2500 g may be lower than in populations with higher mean birth weights. There is evidence for this from the USA in populations living at high altitude (e.g., Colorado, Tables 1 and 3) and from the United Kingdom in populations differing in racial origin (*27*). At present, however, there are insufficient birth-weight-specific mortality data to determine whether, or to what extent, the relative risk of neonatal and post-neonatal death among LBW infants in developing countries differs from that in developed countries.

Many of the factors affecting mortality are interrelated. Few studies have attempted to determine the effect of one factor while controlling for the interrelated factors. In Baltimore, during 1960–64, a cohort of 108 852 single live births of known birth weight were followed for one year after birth. When the effects of birth weight, race, socioeconomic status, maternal age, birth order, and prenatal care were separated, birth weight was the most important factor in neonatal mortality, and factors such as race, socioeconomic status and maternal age were important only because they were related to birth weight (*102*). Likewise birth weight was the most important factor in post-neonatal mortality. However, in this period the other factors (except for race) were also important. In New York City during 1976–78, socioeconomic circumstances were also found to have little effect on the probability of neonatal death once birth weight was controlled (*83*). No comparable analyses from developing countries have been located.

Mortality among preterm versus SGA infants. Although the data are limited, it would appear that in both developed and developing countries preterm infants have a considerably higher risk of neonatal death than term SGA infants of similar birth weight (*9*, *110* and Table 5). The reason for this is the greater difficulty experienced by preterm infants in adapting to the extrauterine environment owing to immaturity of many of the body's systems (*117*).

In the post-neonatal period, preterm infants may also experience higher mortality rates than term SGA infants (Table 5), but the difference is less marked and less consistent than in the neonatal period.

The data on childhood mortality are very limited. However, in New York, term SGA infants appeared to be at slightly greater risk, their 12–23-month mortality rate being 2.7 per 1000 compared with 2.3 for preterm infants (*117*). In Santa Maria Cauqué, term SGA infants had a higher mortality rate during the second, third, and fourth years of life than preterm infants (*68*).

Studies in the USA and United Kingdom have shown that term SGA infants grow more slowly than

preterm infants (*25*, *32*, *81*, *117*), the difference in their mean weight being 0.7 kg at 12 months (*25*, *117*) and 5 kg at 10 years of age (*32*). Slower growth in SGA infants compared with preterm infants has also been reported from New Delhi (*100*). In conclusion, it would seem that preterm infants are at greater risk of death, especially neonatal death, in the first year of life than term SGA infants, but that preterm infants who survive may grow better than SGA infants and have lower mortality rates after 1 year of age.

Association of low birth weight with infant morbidity. At present only limited data are available, although several long-term prospective studies of preterm infants are in progress in developed countries. In Oakland, California, LBW infants did not experience significantly more episodes of acute diseases in the first two years of life than infants of higher birth weight (*116*).

Association of low birth weight with diarrhoea morbidity or mortality. The association, if any, between LBW and diarrhoea morbidity or mortality is poorly documented. In the Inter-American Investigation of Mortality in Childhood (*89*), LBW was examined as an associated cause of diarrhoea mortality, but only in relation to the neonatal period. Of 1269 neonatal diarrhoea deaths recorded in 8 countries, LBW was a contributory cause in 49%, with a range from 28% in Bolivia to 80% in Jamaica. In a prospective study from 1964 to 1972 in the Guatemalan village of Santa Maria Cauqué, LBW infants showed greater rates of diarrhoeal disease and greater prevalence rates of infection with *Shigella*, *Entamoeba histolytica* and *Giardia* in the first six months of life than infants of higher birth weight (*68*, *69*). These findings are not reported in a way that allows diarrhoea incidence by birth weight to be calculated.

Since epidemiological data are limited, an alternative approach is to examine physiological function. It is known that the immune response of LBW infants is severely compromised (*19*, *38*) and is more adversely impaired than that of postnatally malnourished infants (*38*). In addition to defects in cellular immunity, LBW infants have been found to have a significant reduction in maternal–fetal transfer of IgG (*19*, *100*) and impaired synthesis of IgA, IgM, and the C_3 component of complement (*100*). In a follow-up study of 30 LBW infants in New Delhi, impaired immunity was associated with recurrent attacks of diarrhoea in the first 6 months of life. The impairment was most marked in SGA infants (*100*). It may be tentatively concluded from these limited data that LBW infants, especially if they are small for gestational age, may be predisposed to increased diarrhoea morbidity rates. Furthermore, since malnourished infants are more likely than well nourished infants to die from diarrhoea (*33*), it is reasonable to expect that LBW infants, especially if they are SGA, will experience increased diarrhoea mortality rates. Further research is warranted to confirm these tentative conclusions.

Evidence suggests that breast-feeding protects young infants from diarrhoea (*36*). In some countries, especially where babies are born in hospital, a greater proportion of LBW infants may be fed artificially compared with infants of heavier birth weight. Feeding mode may therefore also contribute to an increased risk of diarrhoea among LBW infants.

Conclusions on hypothesis 1. Birth weight is a major determinant of infant mortality and, in developed countries at least, the effect of birth weight on neonatal mortality is independent of socioeconomic status. Where information is available, and this shows considerable local and regional variations, the majority of LBW infants in developed countries are preterm, whereas in developing countries the majority are small for gestational age. Preterm AGA infants suffer higher infant mortality rates than SGA infants, and this difference is especially marked in the neonatal period. On the other hand, preterm AGA infants may grow better post-neonatally than SGA infants.

We have located no satisfactory data on LBW as a determinant of diarrhoea mortality or morbidity. The strong association between LBW and mortality (Tables 3 and 4) makes it likely that there is an association between LBW and diarrhoea mortality in developing countries where diarrhoea is a major cause of infant death. Immunity is severely impaired in LBW infants, especially SGA infants. Data from India and Guatemala indicate that SGA infants may be predisposed to increased diarrhoea morbidity.

Hypothesis 2. *Improving the nutritional status, health or life-style of pregnant women can reduce the prevalence of low birth weight.*

Etiology of low birth weight. Low birth weight is caused by factors that shorten the length of gestation and/or impair fetal growth. Factors affecting the latter are more pertinent to this review since SGA infants probably comprise the majority of low-weight births in developing countries. Some factors, for example altitude, are not amenable to change. Other factors including socioeconomic status, multiple pregnancy, maternal height, and pregravid weight can only be influenced by long-term interventions. In this review, only factors that are more readily amenable to change and might respond to short-term

interventions in developing countries are examined. The factors selected are poor nutritional status, physically demanding work, maternal health, maternal age, birth interval, and tobacco and alcohol consumption. Only the first of these is discussed in any detail.

Nutritional status. There is ample evidence that an inadequate dietary intake during pregnancy adversely affects birth weight. In the conditions of severe food shortage that occurred in parts of Europe during the Second World War, average birth weights fell by 185 g to 600 g (*3*, *28*, *105*).

In developing countries with seasonal food shortages, considerable fluctuations in birth weight occur. In the village of Keneba in the Gambia, for example, the mean monthly weight gains of pregnant women were 0.4 kg in the wet season (July–October) and 1.4 kg in the dry season, and the corresponding prevalences of LBW were 35% and 13% (*86*). In July the average birth weight was 480 g less than in May (*94*). However, the rainy season is not simply a time of food shortage, it is also a period of increased prevalence of maternal infection, including malaria, and a period of increased agricultural activity. The seasonal decrease in birth weight is thus likely to be the result of several adverse factors which together affect both maternal nutritional status and health.

A major focus of maternal and child health programmes has been the provision of additional food to pregnant women. Unfortunately, few such interventions have been evaluated. One exception is the nationwide special supplemental food programme for low-income American women, infants and children (the WIC programme), which encourages clinic attendance and provides individual nutrition counselling in addition to the WIC foods (milk or cheese, eggs, iron-fortified cereal, and fruit juices) through the Food and Nutrition Service of the US Department of Agriculture. This programme has been associated with an increased weight gain in pregnancy, an increase in birth weight (+136 g, if supplemented for more than 6 months), and a decrease in the prevalence of LBW from 10% to 6% (*11*, *29*, *54*). Of the services provided, only food supplementation had a significant effect on birth weight (*54*).

Several small-scale feeding trials have been evaluated and the results of nine such studies are summarized in Table 6. In four of the studies the observed improvement in birth weight was statistically significant although not always large (Mexico, +213 g; Keneba, +120 g; Guatemala, +117 g; and Montreal, +40 g). In the three developing countries where the prevalence of LBW was >15% (the Gambia, Guatemala, and Mexico), supplementation led to a statistically significant reduction in the proportion of low-weight births.[a] In China (Province of Taiwan), the existing prevalence of LBW was low and pre-supplementation birth weights were relatively good, especially if one takes into account maternal short stature (*65*). The participants in this study may therefore not have been at much nutritional risk. It may be concluded that, where maternal nutritional status is poor, food supplementation that effectively increases net intakes can improve birth weights and reduce the prevalence of LBW.

In Harlem (New York City) a decrease in mean birth weight was observed with a high-protein, high-mineral supplement (*99*). Since similar findings have been reported from San Francisco with the same supplement (*2*) and from Motherwell (Scotland) when pregnant women were advised to eat a predominantly protein diet (*44*), caution has been expressed about possible deleterious effects of excessively high protein intakes in pregnancy. The apparent decrease in mean birth weight with a protein-free supplement in Birmingham (England) was probably due to imperfect matching of the groups (*119*).

The provision of a food supplement, however, does not necessarily lead to its consumption. In some societies pregnant women may purposely restrict their intake in anticipation of an easier delivery, and thus traditional dietary customs may limit any effort to improve maternal nutrition, whether by dietary advice or by direct food supplementation. For example, in Project Poshak in India, food collection rates were poor in pregnancy and 90% of the ration which was collected was subsequently dispersed among other family members (*43*). In Colombia where food supplements were provided for each family member, pregnant women consumed only 57% of their allocation. Moreover, the supplement replaced some of their regular diet so that despite very generous rations there was a relatively small increment in net intake (*50*). In contrast, in the Gambia a high uptake of the supplement was achieved which was attributed to its palatability and to the fact that it was offered in the early morning when the women would not normally have eaten at home (*88*). Its high-energy density assisted in achieving a substantial net increase in energy intake.

The magnitude of the response in birth weight to supplementation may appear disappointingly low. However, where the data have been disaggregated, the response among inadequately nourished mothers is substantial. For example, supplementation increased the mean birth weight during the wet season in the Gambia by 225 g and decreased the prevalence of LBW from 28% to 5% (*88*). In Colombia,

[a] Similar results have also been reported from India, where supplementation in the third trimester was associated with a significant increase in birth weight (+170 g) and a 48% reduction in the prevalence of LBW (*129*).

Table 6. Effect of food supplementation on mean birth weight and prevalence of LBW

Country	Place	Habitual daily intake		Daily allocation of supplement		Net increase in energy intake (kcal/day)	Duration of supplementation (weeks)	Increase in mean birth weight (g)	Reduction in LBW births (%)	Dose response g/10 000 kcal or 41.84 MJ[e]	Reference
		kcal	protein (g)	kcal	protein (g)						
Canada	Montreal	2250 (9.41)[a]	68	individualized		—[f]	self-selected	40[b]	16	—[f]	*97*
Colombia	Bogota	1610 (6.74)	35	860 (3.60)[a]	38	155 (0.65)[a]	13	51	21	41	*50, 76*
Gambia	Keneba	1470 (6.15)	—[f]	1000 (4.18)	37	430 (1.80)	24	120[b]	68[c]	17	*86-88*
Guatemala	4 villages	1500 (6.28)	40	self-selected		149 (0.62)	self-selected	117[b]	41[d]	29	*46, 58, 60, 61*
Mexico	Rural areas	1950 (8.16)	50	300 (1.26)	20	275 (1.15)	34	213[b]	80[c]	28	*22, 23*
China (Province of Taiwan)	Sui-Lin	—	—	800 (3.35)	40	—	> 40	16	48	—	*12, 65*
United Kingdom	Aberdeen	2060 (8.62)	70	290 (1.21)	15	189 (0.79)	12	37	—	—	*17*
	Birmingham	—	—	425 (1.78)	0	—	10	−120	—	—	*119*
				425 (1.78)	11	—	10	330	—	—	
USA	Harlem	2060 (8.62)	80	320 (1.34)	6	207 (0.87)	> 10	41	28	—	*98, 99*
				470 (1.97)	40	261 (1.09)	> 10	−32	—	—	

[a] Figures in parentheses are equivalent units in megajoules (MJ), which is the approved SI unit to replace the thermochemical kilocalorie (kcal).
[b] Statistically significant increase in mean birth weight ($P < 0.05$).
[c] Statistically significant decrease in % of LBW births ($P < 0.01$).
[d] Statistically significant decrease in % of LBW births ($P < 0.05$).
[e] Grams of birth weight per 10 000 additional kcal (or 41.84 MJ) consumed.
[f] — denotes data not available.

supplementation increased the mean birth weight by 181 g among mothers of low weight-for-height (*50*). When the Guatemalan data were disaggregated by socioeconomic score, supplementation reduced the prevalence of LBW only among the more disadvantaged mothers. The reduction was from 29% to 13% (*59*). These examples emphasize the importance of targeting food supplements to those most at risk. Unfortunately, relatively little attention has been directed towards identifying meaningful and practical criteria for selecting pregnant women who would benefit from dietary supplementation. Anthropometric indices are likely to be the most appropriate criteria (*46*, *121*). Dynamic criteria such as weight gain are preferable, but the necessity for at least two measurements limits their feasibility.

Energy, rather than protein, appears to be the main factor limiting fetal growth, and the total additional calories consumed during pregnancy seem more important than the trimester in which supplementation is initiated (*62*). Where data permit, dose–response values have been calculated in terms of the mean increase in birth weight for every additional 10 000 kilocalories (41.84 MJ) consumed during pregnancy (Table 6). The average values vary between 17 g and 44 g per 41.84 MJ (10 000 kcal). Where data are disaggregated, the response increases with decreasing nutritional status of the mother.

Space does not permit a full discussion of the possible relationships between other specific nutritional deficiencies and birth weight here. Anaemia in pregnancy is common in developing countries (*5*) and severe anaemia (haemoglobin of < 3.7 mmol/l or 60 g/l) is associated with LBW (*104*). Although there may be a relationship between haematological status and birth weight (*40*, *104*, *122*, *128*), studies in developed countries (*49*) and in India (*109*) suggest that the administration of iron during pregnancy has no detectable effect on birth weight or length of gestation. These studies, however, have not examined the effect of iron supplementation on birth weight in severe anaemia, as opposed to mild anaemia. The relationship between maternal folate status and birth weight is not clear (*96*, *122*, *128*), but folate supplementation may enhance birth weight (*8*, *52*) and further research is warranted. Poor maternal zinc status is associated with SGA births (*72*, *84*). Prenatal supplemental iron or folate may adversely affect maternal zinc status (*47*, *74*, *108*).

Physically demanding work. A seasonal increase in the energy expenditure of pregnant women may have a greater impact on birth weight than a seasonal decrease in energy intake. For example, in Keneba in the Gambia, the decrease in birth weight preceded the decrease in energy intake and mirrored the increase in physical work (*94*), and in the village of Ikwiriri in the United Republic of Tanzania no seasonal decrease in birth weight was observed in 1979 when flood rains delayed field work (*7*). In a review of the pattern of work during pregnancy in 112 traditional societies, in 45% of them the women continued full duties until the onset of labour (*53*).

In the US Collaborative Perinatal Project, continuation of employment during the third trimester was associated with a reduction in mean birth weight of between 150 g and 400 g. The effect was greatest for women whose work involved standing, and those with a low pregravid weight, hypertension, or a low weight gain (*78*). In a Bombay cotton mill during 1925–28, the mean birth weight was 139 g lower among women mill-workers than among the non-working wives of mill-workers, all of whom lived in similar grossly overcrowded conditions. During 1928–29, when there was a general strike for 6 months and the women workers had an enforced rest, the mean birth weight increased by 151 g and the prevalence of LBW (< 5 pounds or 2268 g) decreased from 23% to 13% (*6*). In Dakar, birth weights were found to be relatively low in women involved in strenuous physical work but whose nutritional status was considered adequate (*13*). It is known that exercise and an upright posture adversely affect placental blood flow and it is for this reason that statutory maternity leave was first introduced in the United Kingdom. If exercise is undertaken in the heat, blood has to be diverted to the skin as well as to the muscles, thus reducing placental perfusion still further. Thus certain types of work after mid-pregnancy may impair fetal growth by reducing placental blood flow and/or by affecting energy balance.

In many developing countries it is likely that a reduction in the work load of pregnant women would reduce the prevalence of LBW. Clearly this would involve technological innovations and a radical change in social attitudes and in the work patterns of both men and women (*31*). Changes in social attitudes and work patterns are unlikely to be achieved in the short term.

Maternal health. Untreated maternal infections, hypotension, and hypertension may affect fetal growth. In endemic regions malaria is associated with LBW. In a study in southern Nigeria, 24% of parturient women had malarial infection of the placenta and the mean birth weight of their infants was 145 g lighter than the infants of non-infected women (*14*). Parasitaemia rates are highest among primigravidae (*120*). In the Gambia, the difference in mean birth weight between the infants of infected and non-infected women was approximately 150 g for firstborn infants and 60 g for all other births (*67*). In the Solomon Islands, the mean birth weight rose substantially within months of starting anti-*Anopheles*

spraying (*66*). Between 1969 and 1971 the mean birth weight increased by 252 g for babies of primigravidae and by 153 g for all other babies. The overall prevalence of LBW fell from 21% to 12%. Infections of the urinary tract are associated with preterm delivery (*77*) and with SGA births (*48*). In rural Guatemala, the incidence of urinary tract infection was 27 per 100 pregnancies (*115*). A number of studies have reported a reduction in the prevalence of LBW by antibiotic treatment of pregnant bacteriuric women (*1*). Amniotic fluid infections are common especially in undernourished gravidae, and infection within the amniotic cavity may initiate preterm labour (*75*). Poor maternal nutrition appears to interfere with the normal antibiotic activity of the amniotic fluid. In Ethiopia, antimicrobial activity was absent in 75% of randomly selected urban women at term, possibly as a result of zinc deficiency (*113*), and 31% of women had localized chorioamnionitis at delivery (*79*).

Maternal hypotension and hypertension are associated with reduced uteroplacental perfusion. In the British Perinatal Mortality Survey, severe pre-eclampsia (diastolic pressure of 14.7 kPa (110 mmHg) or more, or of 12 kPa (90 mmHg) or more with proteinuria) was associated with a 3.3 relative risk of a LBW delivery and with a mean birth weight reduction of 225 g (*15*). In Ethiopia, severe growth retardation was found in fetuses whose deaths were ascribed to pre-eclampsia (*112*).

Antenatal care of good quality is likely to improve maternal health and thereby reduce the prevalence of LBW. Such an effect has been documented in India (*80, 103*), the United Republic of Tanzania (*7*), and the USA (*45*). Unfortunately the existing coverage of antenatal services is very low in most developing countries and of the few women who use the services, most do so only in the last trimester.

Maternal age. Teenage mothers have a higher frequency of low-weight births for any given parity (*90*). In 1976 in the USA, teenage mothers had a relative risk of LBW of approximately 1.5 compared with mothers aged 20–24 years (*114*). In New Delhi the relative risk was 1.4 (*91*). A reduction in the proportion of teenage pregnancies should reduce the prevalence of LBW, but will be difficult to achieve in the short term in some societies.

Birth interval. Studies in the United Kingdom (*18*), the USA (Table 7), and Guatemala (*69*) have shown that a short birth interval, especially of < 12 months, is associated with an increased risk of LBW. In developing countries, short birth intervals are becoming more common especially in urbanized areas where reduced breast-feeding is associated with a shortened duration of postpartum amenorrhoea (*118*).

Table 7. Percentage of low-weight births among Black and White populations, by interval since last birth, in 43 States of the USA, 1976[a]

Birth interval (months)	Prevalence of LBW (%)	
	Black	White
< 12	26.9	14.8
12–23	12.1	5.0
24–35	9.9	3.9
36–47	9.7	3.8
⩾ 48	9.8	4.7

[a] All data from ref. *114*.

Tobacco smoking and chewing. It is well established that maternal smoking reduces birth weight (*42*) and that there is a linear dose–effect relationship in which the more cigarettes are smoked, the greater is the reduction (*16, 39*). The putative mechanisms responsible are discussed elsewhere (*26, 51, 57, 63, 64, 73, 127*). Smoking more than 15 cigarettes/day doubles the incidence of LBW. It has been shown that the adverse effect of smoking is independent of social class, maternal age, and parity (*16, 24, 42*). In a recent review, average reductions in birth weight ranging from 120 g to 430 g are reported (*57*). Tobacco chewing also reduces birth weight (*56*), although this has been little studied. In a prospective, randomized experiment (*101*), a specific antismoking campaign directed at pregnant smokers was associated with a significant increase in mean birth weight (+92 g). There was also a 24% reduction in the prevalence of LBW, from 8.9% to 6.8%, although this was not statistically significant.

Alcohol consumption. Animal studies suggest that alcohol is embryotoxic and teratogenic. The 'fetal alcohol syndrome' is found only among infants of mothers who regularly consume over 80 g alcohol/day. Characteristically these infants are growth retarded at birth and show a consistent pattern of congenital anomalies (*107*). Whether more moderate alcohol consumption, before or during pregnancy, adversely affects birth weight is less clear. Failure to allow for confounding variables and difficulties in obtaining accurate drinking histories may have contributed to the apparently conflicting results. A recent prospective investigation of 900 pregnancies in London, which was well controlled for confounding variables, has found that women consuming more than 100 g alcohol/week (1–2 drinks/day), around the time of conception, were more than twice as likely as light drinkers to have a LBW infant (*126*). There was no apparent benefit, in terms of birth weight,

from reducing such drinking once pregnancy was confirmed. The effects of heavy binge drinking are currently being analysed. Moderate drinking (50–100 g alcohol/week) was not associated with a significantly increased risk of LBW.

Conclusions on hypothesis 2. Poor maternal nutrition, certain infections, pre-eclampsia, arduous work after mid-pregnancy, short birth intervals, and teenage pregnancy are likely to be causally associated with LBW in developing countries. Tobacco and alcohol consumption are additional risk factors. It follows, therefore, that interventions that reduce the prevalence of these 'causes' or their relative risks will reduce the prevalence of LBW. Of the interventions examined, maternal food supplementation has been the most studied. If targeted to mothers at nutritional risk, and if the food is consumed in addition to the usual diet, the prevalence of LBW can be expected to be reduced. However, food supplementation can be expensive and the results from carefully supervised feeding trials may be better than those that can be achieved in national programmes. The effect of supplementation with iron, zinc, or folate requires further study.

Hypothesis 3. *Improving the nutritional status, health or life-style of pregnant women can reduce diarrhoea morbidity or mortality rates in young children.*

The only true test of this hypothesis would come from a study in which pregnant women received food supplementation, improved health care, or some other relevant intervention, and where the impact of this on LBW and on the diarrhoea rates in their children was monitored. A randomized controlled trial would be ideal, but might encounter ethical and logistical difficulties. No study of this type has been located, although in the Gambian prenatal supplementation study the preliminary findings[b] show that there has been a sustained improvement in the nutritional status of the wet season cohort. The most likely explanation is that their increased birth weight resulted in fewer, or shorter, episodes of diarrhoea. A few studies have been reported in which food supplementation for pregnant women, combined with other interventions, was introduced and the impact of the combined intervention on diarrhoea rates was recorded. These results cannot be used to test hypothesis 3 because the other interventions, such as food supplementation for infants, are ones that may well have independent effects upon diarrhoea rates. Hypothesis 3 must be examined, therefore, by theoretical calculations of the reductions in diarrhoea morbidity and mortality rates that might be achieved by levels of birth-weight enhancement that may result from improved maternal nutritional status, health or life-style.

Three hypothetical populations are defined. First, a relatively wealthy population having a prevalence rate of LBW of < 10%; we call this population 1. Second, an intermediate population, such as a poor community in a developed country or a more wealthy urban community in a developing country, having a prevalence rate of LBW of 10–20%; we call this population 2. Third, a relatively poor community having a

[b] PRENTICE, A. M. ET AL. *Effect of prenatal supplementation on birth weight and subsequent growth of infants.* Paper presented at the Fourth Asian Congress of Nutrition, Bangkok, 1–4 November 1983.

Table 8. Standardized birth-weight distributions for populations at three different socioeconomic levels

Birth weight (g)	Percentage of live births					
	Population 1 (relatively wealthy) % LBW = < 10		Population 2 (intermediate) % LBW = 10–20		Population 3 (relatively poor) % LBW = > 20	
< 1501	1.0		1.5		1.5	
1501–2000	1.5	7.5	3.0	14.5	5.0	31.5
2001–2500	5.0		10.0		25.0	
2501–3000	20.0		28.0		45.0	
3001–3500	40.0		36.0		20.0	
3501–4000	25.0		17.0		3.0	
> 4000	7.5		4.5		0.5	
Estimated mean birth weight (g)	3200		3000		2700	

Table 9. Standardized relative risks of neonatal mortality and post-neonatal mortality by birth weight compared to birth weight of 2501-3000 g

Birth weight (g)	Relative risk	
	Neonatal mortality[a]	Post-neonatal mortality[b]
< 1501	50.0	6.1
1501-2000	18.0	3.4
2001-2500	4.0	1.8
2501-3000	1.0	1.0
3001-3500	0.5	0.6
3501-4000	0.4	0.5
> 4000	0.6	0.5

[a] Median values from Table 3.
[b] Median values from Table 4.

prevalence rate of LBW of > 20%; we call this population 3. Using the data on birth-weight distributions in Table 1, each of these three populations is assumed to have a birth-weight distribution as set out in Table 8.

The reductions in infant mortality rates in populations 2 and 3 that may result from interventions that increase birth weight can now be calculated on the basis of the following assumptions.

(1) The effect of birth weight on risk of death does not extend beyond the first year of life. This may not be true but the assumption is necessary owing to lack of data. It is a conservative assumption.

(2) A LBW prevention programme in population 3 will shift the birth-weight distribution to that of population 2 (Table 8).

(3) A LBW prevention programme in population 2 will shift the birth-weight distribution to that of population 1 (Table 8). This is much less likely than assumption 2, as discussed below.

(4) The relative risks of neonatal and post-neonatal mortality by birth weight are as set out in Table 9, derived from the median values in Tables 3 and 4. This may bias the relative risk towards that prevailing in developed countries where LBW infants are predominantly preterm. Using the median value may overestimate the impact of a LBW prevention programme in North Arcot for example, where the relative risks appear to be less than the median. Until more data are available, this assumption is unavoidable.

(5) A LBW prevention programme changes the distribution of birth weight (see assumptions 2 and 3) but the neonatal and post-neonatal death rates for a specified birth weight remain constant. In the medium term this will clearly not be true and as LBW prevalence rates decline, so also will birth-weight-specific mortality rates. It is the correct assumption to make here, however, in order to separate out the impact of interventions to increase birth weight from the impact of other curative and preventive interventions.

These calculations do not take full account of the fact that the amenability of LBW to change, and the choice of interventions that will cause that change, depend on three characteristics of the low-weight births under consideration. First, amenability to change and choice of intervention will depend on the degree of LBW. Births of < 1500 g are unlikely to be reduced by the improvements in maternal nutritional status, health and life-style discussed here. To account for this, the prevalence rates of < 1500 g births have been set at 1.0% in population 1, and 1.5% in populations 2 and 3 (Table 8), despite the fact that the rates are actually > 2% among non-whites in the USA (Table 1). Second, amenability to change and choice of intervention will depend on the ratio of preterm to SGA births. SGA births are likely to be more responsive to the interventions discussed here than are preterm births. Third, and closely related to the last point, as the overall LBW prevalence falls, the ratio of preterm to SGA births will rise and so the LBW pattern will become less amenable to change through improvements in maternal nutritional status, health and life-style. Thus, it is likely to be much easier to shift the birth-weight distribution of population 3 to population 2, than to shift that of population 2 to population 1 (Table 8).

No data on the risk of diarrhoeal death by birth weight have been located. It is therefore assumed that the relative risks of diarrhoeal death by birth weight are the same as those for all death (Tables 3, 4 and 9). This assumption is unlikely to be correct for infants of very low birth weight (say, < 1500 g). However, such babies are assumed to make up a small and relatively unchanging proportion of all births in the 3 populations being considered (Table 8). For higher birth weights, and especially for post-neonatal mortality, the assumption that all deaths and diarrhoeal deaths have the same risk pattern by birth weight is not unreasonable and is supported by data from the Dutch famine study where infant diarrhoeal deaths and overall infant mortality increased in a similar manner in the SGA cohort born during the famine (*111*).

The effects of shifting the birth-weight distribution of population 3 to population 2, and that of population 2 to population 1, on the neonatal, post-neonatal, infant, and 0-4-year age group diarrhoea death rates are shown in Table 10. A population 3 to population 2 shift is what might be anticipated by a LBW prevention programme in a poor community in a

Table 10. The impact on diarrhoea mortality rates of shifting the distribution of birth weights[a]

Birth-weight distribution shift[b]	% reduction in diarrhoea			% of 0-4 years diarrhoea deaths that occur in infants	% reduction in diarrhoea mortality among 0-59-month-old children[d]
	Neonatal mortality	Post-neonatal mortality	Infant mortality[c]		
Population 3 to population 2	30	25	26	40	10
				60	16
				80	21
Population 2 to population 1	32	17	19	40	8
				60	11
				80	15

[a] All calculations assume that the relative risks of diarrhoea death by birth weight are the same as the relative risks of all death by birth weight (see text) and are as set out in Table 9.

[b] See Table 8 for the birth-weight distributions of populations 1, 2 and 3.

[c] Calculated by assuming that 14% of infant diarrhoea deaths occur in the neonatal period (median figure obtained in 8 studies).

[d] Calculated by assuming that either 40%, 60% or 80% of diarrhoea deaths in children under 5 years old occur in children under 1 year, and that birth weight has no effect on the risk of diarrhoea death beyond 1 year of age (see text).

developing country. It presumes a reduction in LBW from 31.5% to 14.5% (a 54% reduction, see Table 8), which has been achieved in the Gambia and Mexico (Table 6). It further presumes an increase in mean birth weight of 300 g, something that appears far harder to achieve on the evidence presented in Table 6. A population 2 to population 1 shift is what might be anticipated by a LBW prevention programme in a Third World city or in a relatively wealthy, developing country. It presumes a reduction in LBW from 14.5% to 7.5% (a 48% reduction, see Table 8), which has been achieved in China (Province of Taiwan) (Table 6). It further presumes an increase in mean birth weight of 200 g, something that appears harder to achieve on the evidence of Table 6.

Expected reductions in diarrhoea mortality rates are 30–32% in the neonatal period, 17–25% in the post-neonatal period, and 19–26% for the entire first year of life (Table 10). Expected reductions in diarrhoea mortality rate in the 0–4-year age group are 8–21%, assuming that LBW confers no excess risk of diarrhoea death after 12 months of age (Table 10). This last expected reduction is sensitive to the proportion of 0–4-year diarrhoea deaths that occur in the first year of life. Widely differing proportions are reported; for instance, 90% in Recife, Brazil (*91*), 81% in Latin America (*89*), 68% in Ludhiana, India (*91*), 55% in North Arcot, India (*92*), and around 40% in a number of studies in Asia and Latin America where active surveillance was employed (*106*). Three proportions (40%, 60% and 80%) are adopted for comparison in Table 10.

There is no good evidence to suppose that either a population 3 to population 2, or a population 2 to population 1, birth-weight-distribution shift is achievable on a national scale by interventions in maternal nutrition, health and life-style. As noted above, the second of these shifts is especially unlikely in the short term. The impacts computed in Table 10 are those expected *if* the birth-weight changes under discussion were achieved. Lesser birth-weight increases would result in lesser reductions in mortality.

Conclusion on hypothesis 3. If it were possible to intervene in maternal nutrition, health and life-style in a developing country in a way that reduced the prevalence of LBW from around 30% to around 15% (Table 8), a fall in infant mortality rate of around 26% would be expected (Table 10). The fall in infant diarrhoea mortality rate might be similar. The scarce data on the relative risk of morbidity by birth weight do not allow any comparable computations for morbidity reductions to be made.

FEASIBILITY AND COST

In the consideration of hypothesis 2 above, a range of interventions were shown to be likely to decrease the prevalence of LBW. These interventions would seek to increase energy intake, decrease arduous work, improve antenatal health care, and reduce tobacco and alcohol consumption in pregnant women. Interventions would also seek to discourage teenage pregnancies and increase the birth intervals. We have reviewed five small-scale feeding trials in developing countries (Table 6). We have no know-

ledge of any regional or nationwide programmes for LBW prevention in developing countries using any of the interventions mentioned above that have been evaluated. We can therefore say little about the feasibility and cost of such programmes.

Energy supplementation for pregnant mothers at nutritional risk is perhaps the most likely of the interventions listed above to achieve reductions in LBW prevalence in the short term. However, such an intervention suffers from the very considerable cost, logistical and other disadvantages of all supplementary feeding programmes (*33*). Changes in work patterns and attitudes towards work during pregnancy may be extremely resistant to change in the short term. Antenatal care is gradually improving in most developing countries, and it is unlikely that a LBW prevention programme could significantly accelerate this process. Vigorous educational programmes may be able to reduce tobacco and alcohol intake during pregnancy, but we know of no documented examples of such campaigns in developing countries. Discouraging teenage pregnancy, and promoting longer birth intervals, are part of existing birth control programmes in several developing countries. They should have a beneficial effect upon birth weights but this is secondary to the primary goal of reducing the birth rate.

CONCLUSIONS

A substantial reduction in the prevalence of low birth weight is theoretically possible and would lead to a substantial reduction in infant mortality rate (Table 10). The effect on diarrhoeal mortality or morbidity rates is unknown, however. In this paper it has been assumed that the relative risk of diarrhoeal death by birth weight is the same as that for all death (Table 9). Data are so scarce on the risk of morbidity, diarrhoeal or other, by birth weight that no computations have been possible.

Prospective studies are required that record from birth the diarrhoea morbidity rates, and if circumstances permit, the diarrhoea mortality rates, of groups of infants having known birth weights. These infants should be followed for at least 12 months, and preferably 24 months to determine if LBW confers an excess risk of diarrhoea in the second year of life. The relative risk values obtained may be used to compute the reductions in diarrhoea morbidity and mortality that would follow from a given improvement in birthweight distribution.

At the same time, greater attention should be paid to the problem of LBW in developing countries. This review has confirmed that, whatever its association with diarrhoea, LBW is an important determinant of infant mortality. For the more general goal of reducing infant mortality it is necessary to know more about the nature (preterm vs small for gestational age), etiology, and prevention of LBW in developing countries. In particular, it is necessary to know whether interventions to reduce LBW are feasible at a national or subnational scale in developing countries and whether such interventions are cost-effective in comparison with other strategies for reducing infant mortality rates.

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RÉSUMÉ

INTERVENTIONS CONTRE LES MALADIES DIARRHÉIQUES CHEZ LE JEUNE ENFANT: PRÉVENTION D'UN FAIBLE POIDS DE NAISSAANCE

Le présent article constitue la cinquième mise au point d'une série sur les interventions possibles en vue de réduire la morbidité et la mortalité associées aux maladies diarrhéiques chez les enfants de moins de cinq ans dans les pays en développement. On étudie ici l'influence d'un faible poids de naissance (FPN) sur la morbidité et la mortalité par diarrhées ainsi que les interventions visant à augmenter ce poids. Tout en reconnaissant que l'étiologie du FPN est multifactorielle, l'accent est mis sur les facteurs maternels dont on pense qu'ils ont le plus d'importance dans les pays

en développement et qu'ils sont susceptibles d'évoluer dans un proche avenir, moyennant des interventions convenables.

Sur l'ensemble des naissances, on compte 16% de FPN (< 2500 g). D'après les observations, la majorité des cas de FPN seraient des prématurés dans les pays développés, et des enfants petits par rapport à leur âge gestationnel (PAG) dans les pays en développement. Le poids de naissance conditionne largement la mortalité infantile et, au moins dans les pays développés, son influence sur la mortalité néonatale ne dépend pas de la situation socio-économique. Chez les prématurés de poids normal pour leur âge gestationnel (NAG), on observe un taux de mortalité infantile plus élevé que chez les nourrissons PAG mis à terme, la différence étant particulièrement marquée à la période néonatale. Aucune donnée convaincante n'a pu être trouvée quant au rôle étiologique du FPN dans la morbidité ou la mortalité d'origine diarrhéique. L'association étroite entre FPN et mortalité fait qu'il existe probablement un lien entre FPN et mortalité d'origine diarrhéique dans les pays en développement où les diarrhées sont l'une des grandes causes de mortalité infantile. L'immunité est gravement amoindrie chez les nourrissons de faible poids de naissance, spécialement les nourrissons PAG.

Une nutrition médiocre chez la mère, certaines infections, la néphropathie gravidique, un travail pénible au-delà du milieu de la grossesse, des naissances rapprochées et le jeune âge de la future mère, encore adolescente — tous ces facteurs ont certainement un lien de cause à effet avec le FPN dans les pays en développement. L'usage du tabac et la consommation d'alcool sont des facteurs de risque supplémentaires. Il s'ensuit que les interventions qui rendent ces "causes" moins fréquentes ou qui abaissent le risque relatif correspondant, sont de nature à réduire la prévalence du FPN. Parmi les interventions examinées, l'administration à la mère de suppléments nutritionnels a été la plus étudiée. Cette intervention est en principe efficace si elle vise les femmes en cause du fait de leur nutrition et si les aliments distribués viennent compléter leur ration habituelle. Cependant, la distribution de suppléments nutritionnels peut être coûteuse, et des essais soigneusement supervisés pourraient donner de meilleures résultats que ceux qu'on obtient dans les programmes nationaux. L'effet de suppléments de fer, de zinc ou de folate nécessite des études complémentaires.

Si l'on pouvait agir sur la nutrition, l'état de santé et le mode de vie des mères dans un pays en développement de façon à ramener la prévalence du FPN d'environ 30% à 15%, on devrait obtenir une baisse du taux de mortalité infantile de l'ordre de 26%. Le taux de mortalité infantile par diarrhée devrait enregistrer une chute similaire. Les rares données dont on dispose sur le risque relatif de morbidité associé à un faible poids de naissance ne permettent pas de faire des calculs analogues quant à la réduction à attendre pour le taux de morbidité.

Il est indispensable de réaliser des études prospectives où seront enregistrés dès la naissance le taux de morbidité par diarrhée (et, si les circonstances le permettent, le taux de mortalité correspondant) dans des groupes de nourrissons ayant un faible poids de naissance, de valeur connue. En même temps, il faudra se préoccuper davantage du problème du FPN dans les pays en développement. La présente étude a confirmé que le FPN constitue, quel que soit son lien avec la diarrhée, un déterminant important de la mortalité infantile. S'agissant de l'objectif, plus général, d'un recul de la mortalité infantile, il faudrait en savoir plus sur la nature (prématurés ou enfants petits pour leur âge gestationnel), l'étiologie et la prévention du FPN dans les pays en développement. En particulier, il convient de savoir si les interventions visant à limiter les cas de FPN sont praticables dans ces pays, à l'échelle nationale ou infranationale, et si elles ont un rapport coût/efficacité favorable par comparaison à d'autres stratégies envisageables pour faire reculer la mortalité infantile.

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CH 3.5

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Interventions for the control of diarrhoeal diseases among young children: promotion of personal and domestic hygiene*

R. G. FEACHEM[1]

The effects of improving personal and domestic hygiene on diarrhoea morbidity are reviewed using data from studies in hospitals, day-care centres, and communities. There is evidence that low educational attainment and certain religious customs predispose to diarrhoea, presumably because of behavioural factors. The specific hygiene-related behaviour that has been most studied is hand-washing. Hospital studies suggest that enteric infections can spread via contaminated hands and that hands can be decontaminated by washing with soap and water. Three studies from Bangladesh, the USA, and Guatemala on the impact of hygiene education programmes on diarrhoea are reviewed in detail. Reductions in diarrhoea incidence rates of between 14% and 48% were documented in these studies. Little is known on the impact of hygiene education programmes on diarrhoeas of specific etiology or of their impact on diarrhoea mortality. Information is lacking on the optimal design of such programmes, on their costs, and on their dependence on pre-existing levels of sanitary facilities. The available evidence suggests that hygiene education programmes may be a cost-effective intervention for diarrhoea morbidity reduction. Research is necessary to fill the current gaps in understanding and to clarify the operational aspects of these programmes.

Most of the pathogenic organisms that cause diarrhoea, and all the pathogens that are known to be major causes of diarrhoea in many countries, are transmitted primarily or exclusively by the faecal-oral route. For some enteric pathogens, man is the principal reservoir and thus most transmission originates from human faeces; examples are enterotoxigenic *Escherichia coli*, *Shigella* spp., *Vibrio cholerae*, *Giardia lamblia* and *Entamoeba histolytica*. For other enteric pathogens, animals are important reservoirs and transmission originates from both human and animal faeces; examples are *Campylobacter jejuni*, *Salmonella* spp. and *Yersinia enterocolitica*. For viral agents of diarrhoea the role of animal reservoirs in human disease remains uncertain.

Faecal-oral transmission may be water-borne, food-borne, or direct. Water-borne transmission may occur when water contaminated by faeces is drunk. Food-borne transmission may occur when food contaminated by faeces is eaten. Direct transmission is used here to describe an array of other faecal-oral routes such as via fingers, or objects such as eating utensils, or bed linen, or dirt which may be ingested by young children.

The interruption of water-borne and food-borne transmission requires specific measures which will be reviewed separately. Interrupting direct transmission depends primarily on improved hygiene and on improved facilities, such as better water supplies and latrines that facilitate improved hygiene. Such improved hygienic behaviour may also lessen the chances of contamination of food by food handlers, and may therefore reduce food-borne transmission. Ideally governments will promote educational measures to improve hygiene, as well as water and sanitation projects to improve the physical facilities, in integrated programmes. Such integrated programmes are advocated as part of the International Drinking Water Supply and Sanitation Decade. In practice, however, there are substantial operational differences between hygiene education programmes and water supply and sanitation projects: the two are usually implemented by different ministries and agencies, they require different types of personnel and, in particular, they have very different costs. It is useful therefore to review the effectiveness of hygiene education alone as an intervention for the reduction

* Requests for reprints should be sent to the Director, Diarrhoeal Diseases Control Programme, World Health Organization, 1211 Geneva 27, Switzerland.

[1] Reader in Tropical Public Health Engineering and Head of Department of Tropical Hygiene, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, England.

of diarrhoea morbidity or mortality. This review of the role of hygiene education in diarrhoeal disease control is the fourth in a series of reviews of potential anti-diarrhoea interventions being published in the *Bulletin of the World Health Organization* (*6–9*).

EFFECTIVENESS

For hygiene promotion to be an effective diarrhoea control intervention it must be true that:

either

the transmission of enteric pathogens, and thus the incidence of diarrhoea, are increased by specific behaviours	*hypothesis 1*

and

these specific behaviours can be altered by appropriate hygiene education programmes	*hypothesis 2*

or

appropriate hygiene education programmes can cause behavioural changes which can reduce the transmission of enteric pathogens and thereby reduce diarrhoea morbidity or mortality rates	*hypothesis 3*

Most of the literature on this topic deals with one or more of these specific hypotheses. The potential effectiveness of hygiene education would be suggested by a demonstration either of the correctness of hypotheses 1 and 2 or of the correctness of hypothesis 3. The evidence for and against these hypotheses is examined below.

Hypothesis 1. *The transmission of enteric pathogens, and thus the incidence of diarrhoea, are increased by specific behaviours.*

The anecdotal and descriptive evidence on this topic is extensive; the rigorous and quantified evidence is very limited. The evidence is mainly from three sources:

— studies that show an association between diarrhoea rates and levels of education;

— studies of diarrhoea epidemiology that incidentally comment upon behavioural factors in transmission;

— studies of behaviour and the transmission of enteric pathogens.

These three types of study are considered in turn.

Diarrhoea rates and educational levels. The literature contains many observations that diarrhoea rates are highest in families with the lowest levels of educational attainment. Hygiene and literacy may be closely related (*22*). Such observations in themselves are not useful because families with the lowest educational attainment will tend to be those with the lowest income, poorest housing, most crowding, and worst sanitary facilities. These confounding variables will also promote the transmission of enteric pathogens.

In Bangladesh, Levine et al. (*15*) showed that families with no formal education had a 1.7 times higher incidence of non-cholera diarrhoea, and a 1.8–3.4 times higher incidence of cholera, than families with at least one high-school graduate. Although these comparisons were controlled for tubewell usage, they were not controlled for socioeconomic factors. Levine et al. stated that families with high-school graduates were relatively wealthy, judged by living space, type of house construction, and possession of a radio or watch. An interesting finding from earlier studies on cholera in rural Bangladesh (*17*) was that cholera incidence was higher among Hindus than among Muslims. The incidence among Hindus was 3.0 times higher in 1963–64, 1.1 times higher in 1964–65, and 5.3 times higher in 1965–66 than among Muslims.

This evidence is fragmentary and inconclusive. Studies are required that compare diarrhoea rates by literacy, educational attainment, or religious customs, with the environmental and wealth variables controlled. If significant differences are found, the most likely reason is that the educational or religious differences cause behavioural differences that affect the transmission of enteric pathogens. Detailed anthropological studies will be needed to describe these behavioural differences. If such differences are found, it remains to be shown whether the specific behaviours can be changed by hygiene education in the short-term (rather than by general education in the longer-term or by changing certain religious customs).

Behavioural factors in diarrhoea epidemiology. Numerous studies of diarrhoeal disease epidemiology, and investigations of diarrhoea outbreaks, comment on behavioural factors that may have in-

fluenced the pattern of spread. An exhaustive review of these comments would be unproductive since in general they are speculative and do not firmly associate specific behaviours with specific levels of risk. Most comments in studies from developing countries draw attention to a complex of poverty, ignorance, illiteracy, and crowding and suggest that associated with these circumstances are behaviours that promote the transmission of enteric pathogens. In developed countries the two most commonly mentioned factors are crowding, as may occur among lower socioeconomic groups or during exceptionally cold weather, and poor hygienic practices of young children and those who care for them. The risk of pathogen spread from young children to other members of the family, either directly or via the hands of the parent who cleans them, is stressed repeatedly. The importance of hand-washing by staff in controlling the spread of enteric infections in hospitals, day-care centres, and other institutions is also emphasized.

Behaviour and the transmission of enteric pathogens. The specific behaviours that have received most attention with regard to their role in promoting the transmission of enteric pathogens are water-handling behaviour, food-handling behaviour, and hand-washing. Water-handling and food-handling behaviours will be treated separately in the context of interrupting water-borne and food-borne transmission and will be discussed in later reviews in this series. Here, information on hand-washing is reviewed.

Concern about the possible role of hospital staff in the spread of nosocomial infections has led to several studies of hand-washing behaviour in medical institutions in developed countries. Three such studies are summarized in Table 1. In some settings hand-washing was found to be inadequate, both in frequency and thoroughness. The data from Seattle are particularly striking and suggest a lax attitude to personal hygiene even among those, such as physicians, with a high level of theoretical understanding of the need to maintain scrupulous hygiene in intensive care units. This illustrates that knowledge is not necessarily translated into practice. No studies on hand-washing behaviour in the home, either in developed or developing countries, have been located.

Studies on the occurrence and survival of enteric pathogens on the hands are summarized in Table 2. The hands of hospital staff in developed countries are commonly contaminated and contamination takes place easily during a variety of nursing procedures. The hands of children were readily contaminated by *Shigella sonnei* during shigellosis outbreaks in England. Enteric bacteria on hands survive for at least 3 hours in detectable numbers and can be transferred to food and to other hands. A study in Dhaka (*26*) found that the hands of attendants of hospitalized children with rotavirus diarrhoea were commonly contaminated with rotavirus, and that this contamination was more likely among those who attended younger children.

Studies on the cleansing of hands by washing with water and soap are summarized in Table 3. Hand-washing with water and unmedicated soap removes 90–100% (below the limits of detection) of inoculated bacteria. Washing with water alone removes a considerable but lesser proportion. Some washing procedures with disinfectants do not achieve greater bacterial removals than washing with water and soap. The opinion is often expressed in the literature that the effectiveness of hand-washing is determined more by its thoroughness (time taken and attention to all parts of the hands) than by the types of soap or water used. No data have been located on the effectiveness of hand-washing in the home, or in developing countries, or using other procedures such as rubbing the hands with sand or soil.

The studies summarized in Tables 1–3 are mainly conducted in hospital settings. They indicate that

Table 1. Hand-washing and enteric pathogen transmission: hand-washing behaviour

Study	Findings	Reference
1. Hand-washing frequency by medical staff at an intensive care unit in Seattle, USA, was covertly observed.	Hand-washing occurred after only 41% of patient contacts. Physicians washed after significantly fewer contacts (28%) than nurses (43%).	*1*
2. Hand-washing behaviour among staff at a radiotherapy clinic and a neonatal unit in Helsinki, Finland, was observed over several weeks.	Average hand-washing frequencies per person per 8-hour shift were 10–20 at the radiotherapy clinic and 27–42 at the neonatal unit.	*21*
3. Thoroughness of hand-washing by nurses in England was studied by inviting them to wash with a dye.	89% of nurses missed some part of the hand surface; the most neglected areas were the thumbs, backs of the fingers, and backs of the hands. Right-handed nurses washed the left hand better than the right hand, and vice versa.	*28*

Table 2. Hand-washing and enteric pathogen transmission: occurrence and survival of enteric pathogens on the hands

Study	Findings	Reference
1. The transmission of *Klebsiella* spp. in an intensive care unit in London, England, was studied.	*Klebsiella* were commonly passed from patients (especially patients' hands) to nurses' hands during simple and 'clean' nursing procedures. Over 90% of *Klebsiella* on dry hands could survive for at least 2.5 hours.	*4*
2. Occurrence and survival of *Shigella sonnei* on the hands of children in Southampton, England, during shigellosis outbreaks were investigated.	In 4 studies, 0–49% children had *S. sonnei* on their hands following a visit to the toilet for urination. *S. sonnei* on the hands survived for at least 3 hours. *S. sonnei* in stools passed through double thickness of several brands of toilet paper onto the hands.	*10*
3. Contamination by Gram-negative bacteria of the hands of nurses at an intensive care nursery in Florida, USA, was studied.	151 hand cultures were made from 13 nurses. 86% of cultures and 100% of nurses were positive for Gram-negative bacteria. *Klebsiella pneumoniae* and *Escherichia coli* accounted for 55% of isolates. Evidence was obtained that some Gram-negative bacteria, including *E. coli*, could multiply and persist on the hands of some nurses.	*13*
4. Occurrence and survival of enteric bacteria on finger-tips were studied at the Central Public Health Laboratory in London, England.	*Escherichia coli* were not isolated from the finger-tips of 100 laboratory staff but were isolated from the finger-tips of 12% of butchers in a meat factory. *E. coli* inoculated onto finger-tips decreased by 99% or more after 1 hour. *Salmonella* inoculated onto finger-tips decreased by 96–99.8% after 1 hour. With an initial inoculum of 530 per finger-tip, *S. anatum* were still detectable after 3 hours. *S. anatum* were frequently isolated from corned beef and cooked ham that had been touched for 5 seconds by contaminated finger-tips.	*23*
5. A known number of coliforms were placed on the hands of the author.	After three hours the number of coliforms was "virtually unchanged".	*24*
6. Bacterial contamination of the hands of staff on the general surgical and medical wards at a hospital in New York, USA, was investigated.	Coliforms were found in 23% of hand rinses from physicians, 55% from nurses, 67% from nurse aides, and 67% from other staff. 18% of cultures revealed $> 10^3$ coliforms per 2 hands. 88% of coliforms isolated were in the *Klebsiella–Aerobacter* group and the remainder were *Escherichia coli*. 92% of coliforms isolated were resistant to one or more antibiotics.	*25*
7. Contamination of the hands of the attendants of 147 children under 5 years hospitalized with acute diarrhoea in Dhaka, Bangladesh, was studied. 70 of the children had rotavirus diarrhoea.	Rotavirus antigen was detected in the hand rinses from 79% of the attendants of children with rotavirus diarrhoea, and from 20% of the attendants of children with non-rotavirus diarrhoea.	*26*
8. Effect of baby handling on hand bacteria of nurses was studied in a hospital nursery in New York, USA.	Changing soiled diapers increased the coliforms on the hands by 10^1–10^5-fold.	*27*

knowledge of the importance of hand-washing does not necessarily lead to adequate hand-washing; that hands become easily contaminated by faecal bacteria and viruses even under conditions of good hygiene and high awareness; that enteric bacteria on hands can survive for at least 3 hours and can be transferred to food and other hands; and that washing with soap and water is an effective method of cleansing the hands.

Conclusions on hypothesis 1. Much of the evidence presented bears only indirectly on hypothesis 1. Low educational attainment and certain religious customs predispose to diarrhoea, presumably because of behavioural factors. The specific behaviour that has been most studied is hand-washing. Hospital studies suggest that enteric infections can spread via contaminated hands and that hands can be decontaminated by washing with soap and water. Thus it is probable that

Table 3. Hand-washing and enteric pathogen transmission: cleansing the hands by washing with water and soap

Study	Findings	Reference
1. Experiments were conducted to determine whether ordinary toilet soap, without antibacterial additives, could act as a vehicle for the dissemination of bacteria. Bacteria used were *Escherichia coli*, *Staphylococcus aureus*, two Gram-positive micrococci and *Serratia marcescens*.	Bacteria inoculated onto the surface of soap bars declined in number by at least 5 $\log_{10}$ units in 15 minutes. Washing massively contaminated hands transferred bacteria to the soap bar, but these bacteria did not subsequently transfer to the hands of the next user. Bars of soap under ordinary heavy use did not accumulate appreciable bacterial populations, although bars kept in non-draining trays became somewhat more contaminated than those which were allowed to drain.	*2*
2. Effect of hand-washing with water (rubbing hands together under 45 °C running tap water for 20 seconds) and soap and water (rinsing in warm water for 5 seconds, washing with soap for 15 seconds, rinsing for 5 seconds) on removal of inoculated *Klebsiella* from hands of staff in an intensive care unit was studied.	Washing with water alone removed < 98% of *Klebsiella*. Washing with plain soap removed > 98% of *Klebsiella* in 50% of experiments. Washing with medicated soap removed > 98% of *Klebsiella* in 77% of experiments.	*4*
3. Hands were contaminated with *Staphylococcus aureus* or *Pseudomonas aeruginosa* and then washed for 30 seconds with soap and running water. Bacterial counts were compared with those on unwashed (control) hands that had been similarly contaminated.	Washing with soap and water reduced the geometric mean counts of *S. a.* by 99.7%, and of *P. a.* by 99.8%. Some washing procedures using disinfectants did not remove more bacteria than did washing with soap.	*16*
4. Hands were contaminated with *Staphylococcus aureus* and then rinsed for 30 seconds in distilled water. Bacterial counts were compared with those on unrinsed (control) hands that had been similarly contaminated.	Rinsing with distilled water reduced the geometric mean counts of *S. a.* by 89.8%. Rinsing with hypochlorite solution did not remove significantly more *S. a.* than did distilled water.	*16*
5. Effect of hand-washing (with soap and running water for 15 seconds and then drying on a paper towel) on removing inoculated *Salmonella anatum* from finger-tips was studied.	Proportion of experiments in which *S. anatum* could be isolated from the finger-tips after hand-washing depended on the initial inoculum and was 100% for 10^6 *S. anatum*/finger-tip, 30% for 10^3–10^4 *S. anatum*/finger-tip, and 0% for < 10^3 *S. anatum*/finger-tip.	*23*
6. A variety of experiments on the removal of resident and transient skin flora from hands by scrubbing with soap and water were conducted.	Bacterial removal was not affected by water temperature (24–56 °C), type of soap, drying on a sterile towel or bacteriological water quality. Inoculated bacteria were reduced by 50% after washing with soap and warm water for 30 seconds.	*24*
7. Effect of rapid hand-washing with soap and water, or water alone, on removing naturally acquired coliforms from the hands of nurses in a hospital nursery was studied.	Hand-washing with soap and water removed 67–100% of coliforms (median, 96%). Hand-washing with water alone removed 93–100% of coliforms (median, 98%). The use of disinfectants in rapid hand-washing did not improve coliform removal.	*27*

certain specific behaviours do promote the transmission of enteric pathogens and that failure to wash the hands is one such behaviour.

Hypothesis 2. *Specific behaviours (that promote the transmission of enteric pathogens) can be altered by appropriate hygiene education programmes.*

The literature on the methods and efficacy of hygiene education is mainly comprised of theoretical discussions of approaches likely to succeed or of qualitative descriptions of field experience (*11*, *20*, *29*). Few reports that quantify the impact of a given hygiene education programme on a specific set of personal or domestic hygiene behaviours have been located.

Torún (*30*) reports an evaluation of a hygiene education programme in a village in the Pacific lowlands of Guatemala during 1979–80. The programme was directed at 106 mothers, all of whom had a child under 6 years old; 32 similar mothers acted as controls. The programme consisted of nine 1-hour sessions between educators and groups of mothers

(9–27 per group), using stories and discussions assisted by radio plays and evocative pictures. The mothers were encouraged to reflect upon their hygiene problems and to commit themselves to specific actions. The content of the educational programme covered the recognition and treatment of diarrhoea, excreta disposal, hand-washing, breast-feeding, food hygiene, care of drinking water, and diet. The proportions of mothers giving correct answers to questions on prevention were 56% before the programme, 90% immediately after the programme, and 88% 6 weeks later. A significant increase was observed in the proportion of target families that were judged to have correct hygiene behaviour with respect to diaper disposal, kitchen hygiene, water storage, latrine hygiene, garbage disposal, and child cleanliness. Hygiene practices that would have required expenditure (e.g., improvements to wells and animal enclosures) were not significantly changed. Diarrhoea incidence was reduced in the children of target mothers compared to control mothers, and these data are reviewed below under hypothesis 3.

The body of both theoretical and qualitative evidence, taken together with evidence from other spheres of health education (for instance, smoking, obesity, breast-feeding), strongly suggests that the adoption of hygienic behaviour can be achieved by sustained and culturally appropriate educational programmes. Research is urgently needed to measure the behavioural impact of various types of hygiene education in various cultural and socioeconomic settings. Such research should not prove unduly difficult or expensive.

Hypothesis 3. *Appropriate hygiene education programmes can cause behavioural changes which can reduce the transmission of enteric pathogens and thereby reduce diarrhoea morbidity or mortality rates.*

Three studies (from Bangladesh, the USA, and Guatemala), documenting the impact on diarrhoea rates of hygiene education programmes, have been located. In two cases, Bangladesh and USA, the education focused exclusively on hand-washing, while in the third, in Guatemala, the programme sought to improve several aspects of personal and domestic hygiene.

The Bangladesh study. In Dhaka, Khan (*12*) selected patients with culture-confirmed shigellosis attending a clinic and allocated their families to four groups: a soap and water group that were provided with 2–4 pieces of soap and 1–3 water pitchers and were urged to wash their hands after defecation and before eating; a soap group that was provided with soap only; a water group that was provided with pitchers only; and a control group that was provided with nothing. Rectal swabs of family contacts of the index shigellosis cases in the four groups were obtained daily for 10 days. Contacts infected by the same type of *Shigella* as the index case were termed secondary infections, and those who were also sick (3 or more episodes of diarrhoea or dysentery in 24 hours) were termed secondary cases. The secondary case rate was 2.2% for the soap and water group and 14.2% for the control group, and Khan concluded that the intervention had lowered the secondary case rate by 84%. In the soap and water group, secondary infection rates were significantly higher among those who used less water for washing and bathing. This difference was less apparent among the control group. The reduction in secondary infection rates was less for *Sh. dysenteriae* type 1 than for other *Shigella* species, possibly because of the lower infectious dose of that organism. Attack rates of non-*Shigella* diarrhoea were 37% lower in the soap and water group than in the control group over the 10-day period of surveillance.

To make the reduction in the shigellosis secondary case rate more nearly comparable with the reduction in the non-*Shigella* diarrhoea attack rate, the secondary case rate reduction was converted to an attack rate reduction.[a] On the assumption that the hand-washing promotion had no influence on the incidence rate of index cases, an 84% secondary case rate reduction is equivalent to a 35% reduction in attack rate in the families under study.

The USA study. In Atlanta, GA, Black et al. (*3*) investigated the impact of hand-washing on diarrhoea incidence in four day-care centres. Two groups of children, one aged 6–17 months and the other aged 18–29 months, were studied at each day-care centre. Two of the centres were randomly selected to receive a hand-washing promotion campaign which encouraged staff to wash their hands after arriving at the centre, before handling food, and after helping a child to use the toilet or using the toilet themselves. When children entered the centre, used a toilet, had their diapers changed, or were prepared to eat, staff washed the children's hands using bar soap and paper towels. Children using the toilet were supervised by staff to ensure that they did not place their hands in their mouths. These practices were rigorously monitored. The other two day-care centres received no hygiene promotion and served as controls. It had been observed, prior to this investigation, that the practice of hand-washing and of toilet supervision of young children in these centres was generally lax. The incidence of diarrhoea among the selected children in the four centres was monitored for 10 months; this incidence among children aged 6–29 months was reduced

[a] Assumptions and computations used to make this conversion are available on request from the author.

Table 4. The effect of hygiene education on diarrhoea incidence and the percentage of days ill with diarrhoea in a village in Guatemala[a]

Age group (months)	Full year[b] or peak diarrhoea season[c]	Target or control group	Diarrhoea incidence			Proportion of days ill		
			Mean number of children studied per month	Mean monthly incidence (episodes/100 children/month)	Percentage reduction in incidence	Mean number of child-days studied per month	Mean monthly % of days with diarrhoea[d]	Percentage reduction in % of days with diarrhoea
0–23	Full year	Target	49	36	14	1433	4.5	24
		Control	32	42		906	5.9	
	Peak season	Target	60	38	36	1752	4.1	55
		Control	32	59		872	9.2	
0–71	Full year	Target	152	25	14	4457	3.0	12
		Control	92	29		2577	3.4	
	Peak season	Target	185	25	32	5378	2.7	48
		Control	82	37		2253	5.2	

[a] Reanalysis of data from Torún (*30*).
[b] September 1979 to August 1980.
[c] March–June 1980.
[d] (Number of child-days with diarrhoea × 100) – Total number of child-days observed.

by 48% in the hand-washing day-care centres compared with the control centres.

The Guatemalan study. In Florida Aceituno, a village in the Pacific lowlands of Guatemala, Torún (*30*) promoted health awareness and hygienic behaviour among mothers and studied the impact on their knowledge and behaviour and the effect on diarrhoea rates in their children under 6 years old. The promotion, and its impact on knowledge and hygienic practice, are reviewed above under hypothesis 2. The impact on diarrhoea rates in children is summarized in Table 4. The target group comprised the children of 106 mothers who participated in the educational programme, and the control group comprised the children of 32 mothers who did not participate. Twelve (38%) of the 32 control mothers were of above average socioeconomic status, being the wives of store-owners, preachers or community leaders. The impact on the proportion of days with diarrhoea (a measure combining possible impacts on incidence and duration of episodes) was higher than the impact on incidence. For both impact measures, impact was 2–4 times greater in the peak diarrhoea season (March to June) than throughout the whole year.

Conclusions on hypothesis 3. These 3 studies from Bangladesh, the USA, and Guatemala provide 5 measures of the impact of hygiene education on diarrhoea rates:

— a 35% reduction in the incidence rate of shigellosis among all ages in urban families in Bangladesh;
— a 37% reduction in the incidence rate of non-*Shigella* diarrhoea among all ages in urban families in Bangladesh;
— a 48% reduction in the incidence rate of all diarrhoea among children aged 6–29 months in day-care centres in the USA;
— a 14% reduction in the incidence rate of all diarrhoea among children aged 0–71 months throughout the year in a Guatemalan village;
— a 32–36% reduction in the incidence rate of all diarrhoea among children aged 0–71 months during the peak diarrhoea season in a Guatemalan village.

Thus the reduction of diarrhoea incidence rate to be anticipated from hygiene education lies in the range 14–48%. Other studies support the general contention that hygiene education can reduce diarrhoea

rates, but do not allow a calculation of the reduction in incidence achieved by a clearly defined educational intervention (*14*, *18*, *19*).

It might be supposed that the commonness of direct person-to-person transmission of *Shigella* would make shigellosis especially sensitive to reduction by hand-washing. The evidence presented here does not support this. First, the computed reduction in the shigellosis incidence rate in Dhaka was 35%, whereas in the same families the reduction in the incidence rate of non-*Shigella* diarrhoea was 37%. Second, in the Atlanta study a 48% reduction was recorded and, out of 85 diarrhoea stools cultured, none contained *Shigella*.

The three studies summarized above suggest that hygiene education, especially hand-washing promotion, has a marked impact on diarrhoea morbidity rates. These studies should be repeated in different socioeconomic and environmental settings and should also quantify the impact on diarrhoea due to rotavirus, enterotoxigenic *Escherichia coli*, *Campylobacter jejuni*, *Shigella*, *Giardia lamblia* and other agents that are of known local importance.

FEASIBILITY AND COST

There is such little documented experience of hygiene education programmes that their feasibility is difficult to judge and their costs are unknown. Experience with other types of health education suggests that such programmes are feasible on either a national or local level and that they can employ a combination of mass media techniques and direct interaction between target families and hygiene promoters (*5*). Costs of hygiene education are probably low compared to some other interventions for diarrhoea morbidity reduction—such as the provision of improved water supplies and sanitation facilities. The effectiveness of hygiene education may depend, however, upon the presence of such facilities. In Dhaka the provision of soap, which would be costly on a continuing basis, may have been an essential part of the intervention, and in Atlanta modern facilities for washing and defecation were already available. Operational research is needed to clarify the most effective and feasible types of hygiene education programme, to detail their costs, and to assess their dependence on pre-existing levels of sanitary facilities.

CONCLUSIONS

Interest in the role of education in disease control has increased considerably in recent years. It is probable that better educated communities enjoy relative protection against several diseases compared to less educated, but otherwise similar communities. This protection may be conferred both by general education (as measured, for instance, by school attendance, adult literacy or education of heads of households) and by disease-specific education. Disease-specific education can be preventive or therapeutic in content.

The evidence marshalled in this paper suggests that hygiene education can improve hygiene and can reduce diarrhoea morbidity rates by 14–48%. These are hopeful findings. Many countries, especially in sub-Saharan Africa and Asia, are having extreme difficulty in sustaining the development of their health infrastructure. In the water and sanitation sector, for instance, the rate of construction of new projects barely keeps pace with population growth and the rate of breakdown is alarming. In these circumstances, educational interventions appear especially attractive. They may be cheap compared to infrastructure projects and they may achieve lasting changes in health-related behaviour. Most importantly, as indicated by this review, they may achieve substantial impacts.

Hygiene education programmes are being conducted in many countries and should continue. Countries not having such programmes should seriously consider launching them. Research is necessary, however, to improve the cost-effectiveness of hygiene education. This research is of three main types. First, more information is needed on the associations between specific behaviours and risks of diarrhoea morbidity and mortality of known etiology. Second, operational research is needed to clarify the most effective and feasible types of hygiene education programme, to detail their costs, and to assess their dependence on pre-existing levels of sanitary facilities. Third, impact studies should be conducted to clarify the impact on diarrhoea of carefully designed hygiene education programmes. These impact studies should be etiology-specific and, where possible, should document impacts on diarrhoea mortality rates as well as morbidity rates.

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RÉSUMÉ

LUTTE CONTRE LES MALADIES DIARRHÉIQUES CHEZ LES JEUNES ENFANTS: PROMOTION DE L'HYGIÈNE PERSONNELLE ET DOMESTIQUE

Cet article est le quatrième d'une série portant sur les mesures qui permettraient de réduire la mortalité et la morbidité par diarrhée chez les enfants de moins de 5 ans dans les pays en développement. On a étudié les effets d'une meilleure hygiène personnelle et domestique sur la morbidité par diarrhée en se basant sur des données recueillies dans des hôpitaux, des garderies d'enfants et des collectivités. Ces données montrent qu'un faible niveau d'instruction et certaines coutumes religieuses prédisposent aux maladies diarrhéiques, probablement en raison de certains facteurs comportementaux. La pratique d'hygiène qui a été le plus étudiée à cet égard est celle qui consiste à se laver les mains. Les études faites en milieu hospitalier démontrent que les infections intestinales peuvent être propagées par des mains contaminées et que l'on peut éliminer ce risque en se lavant les mains à l'eau et au savon. Trois études faites au Bangladesh, aux Etats-Unis d'Amérique et au Guatemala sur l'impact que les programmes de promotion de l'hygiène ont sur la diarrhée sont passées en revue dans l'article. Ces études ont mis en évidence des réductions des taux de morbidité par diarrhée allant de 14% à 48%. On sait peu de chose des effets des programmes d'hygiène sur les diarrhées d'étiologie déterminée ou sur la mortalité par diarrhée. On ne dispose pas non plus de renseignements sur la conception optimale de tels programmes, sur leurs coûts, non plus que sur la mesure dans laquelle leur succès dépend de l'existence préalable d'installations sanitaires. D'après les données disponibles ces programmes constituent probablement une mesure d'un bon rapport coût-efficacité pour la réduction de la morbidité par diarrhée. Des recherches doivent être faites pour combler les lacunes existantes dans les connaissances et pour éclairer les aspects opérationnels des programmes d'éducation en matière d'hygiène.

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Interventions for the control of diarrhoeal diseases among young children: chemoprophylaxis*

I. DE ZOYSA[1] & R. G. FEACHEM[2]

A number of situations place young children at increased risk of diarrhoea. Among these, the best documented in developing countries is contact with a diarrhoea case in a family or household. The most common application of chemoprophylaxis in developing countries is to prevent cholera or shigellosis among household contacts of known cases. There is little evidence that chemoprophylaxis is effective in reducing diarrhoea morbidity and mortality, except perhaps in travellers. Theoretical calculations in this paper (based on optimistic assumptions) suggest that chemoprophylaxis of household contacts of known cholera cases in Bangladesh might reduce overall diarrhoea incidence rates in children under 5 years of age by 0.02–0.06% and diarrhoea mortality rates by 0.4–1.2%. Chemoprophylaxis of household contacts of known shigellosis cases might reduce overall diarrhoea incidence rates by 0.15–0.35% and diarrhoea mortality rates by 0.3–0.7% in the same age group. The correct identification of index cases of cholera and shigellosis, followed by the rapid distribution of drugs to their household contacts, requires skills and resources that are scarce in the developing countries. Chemoprophylaxis can contribute to the widespread emergence and dissemination of antimicrobial resistance. The available evidence suggests that chemoprophylaxis is not feasible in many settings and that, even if successfully implemented, it is not a cost-effective intervention for national diarrhoeal diseases control programmes.

The main application of drugs in the control of diarrhoeal diseases is in the treatment of selected cases in order to reduce the duration and severity of illness and prevent death. Additionally, because the duration of excretion of the infectious agent may sometimes be reduced, mass chemotherapy, or the widespread administration of drugs to cases and to infected asymptomatic persons, has been recommended (*90*) for the purpose of reducing the pool of excreters and thereby the potential for transmission. Drugs may also be used to protect uninfected individuals from infection or illness. In this way, antimicrobials have been given prophylactically to individuals at high risk, such as close contacts of known cases or travellers to endemic areas. In practice, mass chemotherapy and individual chemoprophylaxis repeated on a large scale merge into each other because the presence of infection is not always ascertained or recognized.

In this review, we define chemoprophylaxis of diarrhoea as the administration of drugs to persons exposed to a recognized risk, whether infected or not, to prevent diarrhoea in these persons and to reduce the sources of infection. We consider here the role of chemoprophylaxis in national programmes to reduce diarrhoea morbidity and mortality among children under 5 years of age. This paper is the sixth in a series of reviews of potential anti-diarrhoea interventions published in the *Bulletin of the World Health Organization* (*3, 38-42*).

EFFECTIVENESS

For chemoprophylaxis to be an effective intervention to control diarrhoeal diseases it must be true that:

either

a considerable proportion of diarrhoea morbidity or mortality in young children occurs in children who are exposed to a recognized risk, such as contact with a known case	*hypothesis 1*

* Requests for reprints should be sent to the Director, Diarrhoeal Diseases Control Programme, World Health Organization, 1211 Geneva 27, Switzerland.

[1] Save the Children Fund Research Fellow, Department of Tropical Hygiene, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, England.

[2] Reader in Tropical Public Health Engineering and Head of Department of Tropical Hygiene, London School of Hygiene and Tropical Medicine, London, England.

Table 1. Additional cases and infections among household contacts of index cases having diarrhoea of known etiology

Etiology of index case	Country	Age group of contacts (years)	Case rate (%)	Infection rate (%)	Reference
Enterotoxigenic *Escherichia coli*					
ST/LT strains	Bangladesh	0-1	21	29	*10*
		2-4	10	23	
		All ages	4	11	
ST strains		0-1	22	22	
		2-4	10	15	
		All ages	4	10	
All strains	Thailand	0-4	8	42	*34*
		All ages	1	9	
Giardia lamblia	Canada	All ages	2-5	7-13	*70*
	USA	All ages	17	ND[a]	*119*
Norwalk agent	USA	All ages	30-32	ND[a]	*1*
	USA	0-4	40	ND[a]	*5*
		All ages	19	ND[a]	
Rotavirus	Canada	All ages	21	46	*147*
	New Zealand	0-12	66	75	*55*
		All ages	38	46	
	Norway	0-14	62	62	*59*
		All ages	36	44	
	Sweden	0-12	15	22	*151*
		All ages	13	24	
	USA	Adults	8	35	*66*
	USA	Adults	8	55	*78*
	USA	Adults	71	ND[a]	*121*
	USA	All ages	15	ND[a]	*119*
Salmonella spp.	United Kingdom	0-14	24	ND[a]	*149*
		All ages	18	ND[a]	
	USA	0-4	30	48	*124*
		All ages	19	35	
Shigella dysenteriae type 1	Bangladesh	0-4	31	31	*76*
		All ages	13	20	
	Bangladesh	0-4	11	11	*77*
		All ages	4	7	
Shigella flexneri	Bangladesh	0-4	0	11	*75*
		All ages	4	21	
	Bangladesh	0-4	33	50	*77*
		All ages	13	32	
	Marshall Islands	All ages	6	ND[a]	*144*
Shigella flexneri & sonnei	USA	0-4	68	ND[a]	*103*
		All ages	56	ND[a]	
	USA	0-14	50	40	*111*
		All ages	36	31	

Table 1 (*continued*)

Etiology of index case	Country	Age group of contracts (years)	Case rate (%)	Infection rate (%)	Reference
Shigella sonnei	United Kingdom	0-7	34	45	*23*
		All ages	16	33	
	USA	0-4	81	ND[a]	*86*
		All ages	51	ND[a]	
	USA	0-5	45-54	ND[a]	*157*
		All ages	27-36	ND[a]	
	USA	All ages	46	ND[a]	*146*
Shigella spp.	Bangladesh	0-4	24	ND[a]	*73*
		All ages	14	ND[a]	
	Bangladesh	All ages	14	32	*71*
	USA	All ages	26	ND[a]	*119*
Vibrio cholerae					
Classical	Bangladesh[b]	All ages	4-16	11-24	*37*
El Tor	Six countries[b]	All ages	2-25	4-32	

[a] No data.

[b] Feachem (*37*) reviewed 20 studies of cholera attack rates in households of index cases in Bangladesh, India, Hong Kong, Israel, Philippines and China (Province of Taiwan).

and

individuals receiving chemoprophylaxis have lower diarrhoea morbidity rates or mortality rates or severity than otherwise similar individuals	*hypothesis 2*

or

chemoprophylaxis in young children exposed to a recognized risk, such as contact with a known case, can reduce overall diarrhoea morbidity rates or mortality rates or severity in young children	*hypothesis 3*

The potential effectiveness of chemoprophylaxis would be suggested by a demonstration either of the correctness of hypotheses 1 and 2 or of the correctness of hypothesis 3. We examine below the evidence for and against the three hypotheses and we consider the magnitude of reductions in diarrhoea morbidity and mortality in young children that may be achieved by chemoprophylactic measures.

Hypothesis 1. *A considerable proportion of diarrhoea morbidity or mortality in young children occurs in children who are exposed to a recognized risk, such as contact with a known case.*

Several recognized situations place young children at increased risk of diarrhoea. We describe here these high-risk situations and consider their significance with regard to overall diarrhoea morbidity and mortality in young children.

Contact with a known case in the family or household. Numerous studies have been conducted on the transmission of diarrhoeal diseases within households. Data on additional cases and infections among household contacts of a known index case are set out in Table 1 (in this context, the index case is the first recognized case in the household). These studies used different methods. Most were prospective, with observation periods ranging from 1 to 65 days. All index cases had diarrhoea of known etiology and, in some studies, only cases and infections caused by the same organism as the index case were included in the analysis. In other studies microbiological surveillance of contacts was not carried out and all additional cases of diarrhoea were included.

All additional cases and infections among household contacts following the identification of an index case were recorded and therefore both co-primaries and secondaries are included. We are concerned here with the risk of disease among contacts after identification of an index case and it is of no

importance whether the additional cases and infections resulted from a common-source exposure or secondary spread. The terms additional case and additional infection, rather than secondary case and secondary infection, are used throughout this paper.

Additional case rates among household contacts ranged from 1% to 71% and additional infection rates ranged from 4% to 55%. Both rates tended to be higher in the younger age groups. When infected, young children were also more likely to have symptoms than older children and adults. Not only were young children at greater risk of contracting diarrhoea after introduction of the disease into the household, but they also played a major role in the introduction and spread of the disease in the household (*10, 52, 74, 77, 95, 149, 157*).

Household contacts, therefore, are at considerable risk of contracting diarrhoea after identification of an index case. This risk is highest immediately after onset of diarrhoea in the index case, and wanes rapidly thereafter. Among household contacts of known cholera cases, 12–43% of additional cases were identified on the first of 10 days of observation and 85–88% by the sixth day (*8, 95, 116, 139*).

In the above studies, the household was the unit of investigation and it was usually assumed that all household contacts were members of a single family. Increased risk of cholera, enterotoxigenic *Escherichia coli* (ETEC) diarrhoea, and shigellosis has also been reported among persons in the same cluster of houses or neighbourhood as an index case (*18, 34, 61*).

Attendance at day-care centres and schools. A number of studies from industrial countries have examined the role of day-care centres and schools in the spread of diarrhoeal diseases. It has been shown that children attending these centres have a higher risk of contracting diarrhoea than children who remain at home (*9, 25, 28*). Black et al. (*11*) found that children were at increased risk of diarrhoea two to four weeks after enrolment in a day-care centre, which suggests that illness follows contact with other infected or ill children. Investigations within day-care centres have shown a pattern of repeated outbreaks caused by a variety of pathogens and sometimes having high attack rates (Table 2). Studies from the United Kingdom and North America provide evidence that young children in close contact with other children in day-care centres or schools play a major role in introducing diarrhoea into their households and spreading it to other young children (*9, 23, 25, 70, 119, 146, 157, 158*).

No prospective studies of this kind from developing countries have been located. Outbreaks of diarrhoeal disease in day-care centres and schools have been described in countries such as Brazil (*145*) and China (*136*), and it is probable that day-care centres, schools and informal neighbourhood play groups where many children congregate constitute high-risk situations for children everywhere.

Table 2. Attack rates during diarrhoea outbreaks recorded in day-care centres

Etiology	Country	Attack rate (%)	Reference
Astrovirus	Japan	52	*80*
Campylobacter jejuni	Belgium	20-50	*83*
Clostridium difficile	USA	20-58	*79*
Giardia lamblia	Canada	20-39	*70*
	USA	27-35	*9*
	USA	17	*119*
Rotavirus	Belgium	58-78	*43*
	USA	100	*121*
	USA	71	*119*
Shigella spp.	United Kingdom	51	*150*
	USA	73	*48*
	USA	38-51	*158*
	USA	33	*119*
	USA	36-50	*146*
Multiple etiologies	USA	51-57	*119*
	USA	14-92	*35*

Contact with a known case in institutions and hospitals. Institutions such as residential homes for children and institutions for the mentally retarded are associated with a high risk of diarrhoeal disease in industrial countries, where diarrhoea incidence rates are low in the community. Despite the prophylactic and therapeutic use of drugs and the application of isolation techniques, diarrhoeal diseases (particularly shigellosis, giardiasis and amoebiasis) continue to be a significant health problem among institutionalized children in these countries. Children are at highest risk of infection and illness shortly after admission (*19, 29*).

Hospital-acquired diarrhoeal diseases are well documented in industrial countries and may well represent a significant problem in developing countries. In a recent review of publications on nosocomial infections originating from developing countries (*159*), most reported diarrhoea outbreaks in nurseries for premature babies and paediatric wards. Hospital outbreaks may be serious (*115*) and may lead to considerable disruption of patient services (*81*). In industrial countries at least, a considerable

proportion of the diarrhoeal diseases treated in hospital may be nosocomially acquired (*100, 113, 127, 140*). The etiological agent implicated is often rotavirus (*127*), reflecting its importance as a cause for hospitalization among young children.

Importance of these high-risk situations with regard to overall diarrhoea morbidity and mortality. We have described various situations associated with a high risk for diarrhoea, but it is not clear, from the evidence presented so far, what proportion of all diarrhoea morbidity and mortality occurs in these situations. There are limited data on the importance of these high-risk situations in the epidemiology of cholera and shigellosis. We here summarize some of these reports:

—*Cholera.* Detailed studies from Hong Kong, China (Province of Taiwan), and the Philippines suggest that cholera did not spread easily, if at all, within households or among households in a community (*44, 90, 104, 118, 148, 154, 164*). Reported cases were in general sporadic, dispersed throughout the community, and contact-tracing identified few additional cases or infections. In Bangladesh, on the other hand, active transmission within households and from household to household within neighbourhoods has been reported and most cases tended to appear in short family or community outbreaks in urban (*95*) and rural areas (*106, 138*). A recent report from Tanzania (*99*) has documented the role of a hospital in the spread of cholera in an urban centre.

—*Shigellosis.* Data from industrial countries suggest that young children attending day-care centres and schools may play a major role in the spread of shigellosis to the community at large by spreading infection in their own households and from household to household (*103, 126, 146, 150, 157, 158*). Institutions, on the other hand, have not been demonstrated to be a source of infection for the community at large. Shigellosis in institutions may, nonetheless, represent a substantial proportion of all cases (*20, 123*). Data from developing countries on the mode of spread of shigellosis through communities are limited to epidemic situations in which whole communities are suddenly at high risk of diarrhoeal disease. High attack rates and death rates have been recorded (*94, 120*) but clustering by household or neighbourhood does not appear to be prominent (*47, 144*).

Conclusions on hypothesis 1. We have described several situations that place young children at increased risk of diarrhoea. Among these, the best documented in developing countries is contact with a known case in a family or household. The most common application for chemoprophylaxis in

Table 3. Detectable index and additional cholera cases for various values of hospitalization rate, household size and additional case rate

Hospitalization rate (%)	Household size (persons)	Additional case rate[a] (%)	No. of detectable index cases per 100 cases[b]	No. of detectable additional cases per 100 cases[c]	No. of detectable index plus additional cases per 100 cases
30	6	5	24	6	30
30	6	15	17	13	30
30	6	25	13	17	30
30	10	5	21	9	30
30	10	15	13	17	30
30	10	25	9	21	30
50	6	5	40	10	50
50	6	15	29	21	50
50	6	25	22	28	50
50	10	5	34	16	50
50	10	15	21	29	50
50	10	25	15	35	50

[a] See Table 1.

[b] A detectable index case is an index case who is hospitalized.

[c] A detectable additional case is one occurring in the household of a detectable index case in the 10 days following the reporting of the index case.

Table 4. Detectable index and additional shigellosis cases for various values of hospitalization rate, household size and additional case rate

Hospitalization rate (%)	Household size (persons)	Additional case rate[a] (%)	No. of detectable index cases per 100 cases[b]	No. of detectable additional cases per 100 cases[c]	No. of detectable index plus additional cases per 100 cases
5	6	20	2.5	2.5	5.0
5	6	30	2.0	3.0	5.0
5	6	40	1.7	3.3	5.0
5	10	20	1.8	3.2	5.0
5	10	30	1.4	3.6	5.0
5	10	40	1.1	3.9	5.0
10	6	20	5.0	5.0	10.0
10	6	30	4.0	6.0	10.0
10	6	40	3.3	6.7	10.0
10	10	20	3.6	6.4	10.0
10	10	30	2.7	7.3	10.0
10	10	40	2.2	7.8	10.0

[a] See Table 1.

[b] A detectable index case is an index case who is hospitalized.

[c] A detectable additional case is one occurring in the household of a detectable index case in the 10 days following the reporting of the index case.

developing countries is to prevent cholera or shigellosis among household contacts of known cases. We here estimate on a theoretical basis the proportion of all cholera and shigellosis cases that occurs among household contacts of known cases, and is thus potentially preventable by chemoprophylaxis.

In most circumstances, a case of cholera or shigellosis will only be identified if he or she is hospitalized. The calculations for cholera are set out in Table 3.[a] Data from Bangladesh and the Philippines indicate that hospitalization rates for cholera vary between 23% and 74% (*4, 6, 72, 74, 92, 105, 116, 160, 161*). Hospitalization rates of 30% and 50% are adopted in Table 3. Two household sizes, comprising 6 and 10 persons, are used. Six is approximately the mean family size in many developing countries while ten represents the larger extended families, or households comprising, on average, just under two families. Three additional cholera case rates (5%, 15% and 25%) are adopted on the basis of data summarized in Table 1. The proportions of all cholera cases that are detectable additional cholera cases are 6–21% for a hospitalization rate of 30% and 10–35% for a hospitalization rate of 50%.

[a] The formula used to make these calculations is available on request from R.G.F.

Similar calculations for shigellosis are presented in Table 4.[a] A hospitalization rate for shigellosis of 8% has been reported from rural Bangladesh (*13, 14*) and rates of 5% and 10% are used in Table 4. Three additional shigellosis case rates (20%, 30% and 40%) are adopted on the basis of data summarized in Table 1. The proportions of all shigellosis cases that are detectable additional shigellosis cases are 2.5–3.9% for a hospitalization rate of 5%, and 5.0–7.8% for a hospitalization rate of 10%.

The proportions of all cases that are detectable additional cases, and thus potentially preventable by chemoprophylaxis, are 6–35% for cholera and 2.5–7.8% for shigellosis. These proportions are correlated both with the additional case rate and with the hospitalization rate. Thus for shigellosis, despite the fact that additional case rates are high (20–40%), the proportion of detectable additional cases is low because the hospitalization rates are low (5–10%). Hospitalization rates depend on the severity of the symptoms and on the hospital facilities available in the area. The hospitalization rates adopted in Tables 3 and 4 are mainly derived from studies in the Matlab area of Bangladesh. The longstanding presence of a hospital specializing in acute diarrhoeal diseases, and the availability of ambulance services in this area, may lead to higher hospitalization rates than in most other rural areas of developing countries.

Table 5. Summary of trials of chemoprophylaxis among household contacts of cholera cases

Country (place)	Period of follow-up	Drug	Dosage	Results		Reference
				Proportion of household contacts who excreted *V. cholerae* (%)	Proportion of samples from household contacts which were positive for *V. cholerae* (%)	
Bangladesh (Dhaka)	10 days	Tetracycline	4 doses daily × 5 days	0	–	*91*
			Single dose daily × 5 days	1	–	
			Single dose	8	–	
		Placebo		13	–	
India[a] (Calcutta)	10 days	Tetracycline	2 doses daily × 3 days	–	1.5	*62*
		Placebo		–	3	
India (Calcutta)	15 days	Sulfadoxine	Single dose	19[b]	3	*24*
		Tetracycline	2 doses daily × 3 days	21[b]	3	
		Placebo		42[b]	7	
India (Calcutta)	10 days	Doxycycline	Single dose	15[c]	2	*134*
		Placebo		23[c]	4	

[a] *V. cholerae* was isolated from only 60% of index cases.

[b] Excluding contacts infected only on day 1 but including contacts infected on day 1 and on subsequent days.

[c] Excluding contacts infected on day 1.

Hypothesis 2. *Individuals receiving chemoprophylaxis have lower diarrhoea morbidity rates or mortality rates or severity than otherwise similar individuals.*

Chemoprophylaxis of diarrhoea has been recommended and used in numerous situations: to limit the spread of cholera epidemics (*22, 46, 90, 98*), to control shigellosis in institutions, such as institutions for the mentally retarded in the USA (*7, 49, 50, 84, 163*), and to prevent travellers' diarrhoea (*141*). Yet, despite such widespread use, few controlled trials have been conducted to assess the effectiveness of chemoprophylaxis in limiting transmission and reducing diarrhoea morbidity and mortality. The evidence is mainly from three sources:

—studies of chemoprophylaxis among household contacts of cholera cases;
—studies of the prolonged use of antimicrobials to prevent infections in young children;
—studies of chemoprophylaxis of travellers' diarrhoea.

These three types of studies are considered in turn.

Chemoprophylaxis among household contacts of cholera cases. Four studies, one from Bangladesh and three from India, have assessed the impact of chemoprophylaxis on infection among household contacts of a cholera index case (*24, 62, 91, 134*). Different methods were used to analyse the data but the study design was similar in all cases. Families of hospitalized cholera cases were assigned to one of various drug groups or to a control group. Household contacts were followed bacteriologically over a period of 10–15 days. Clinical information was reported in only one study (*62*) where it is stated that all *Vibrio cholerae* excreters were healthy. These studies therefore assessed the effect of chemoprophylaxis on the duration of excretion of *V. cholerae* among infected contacts and on transmission of infection within the household. They did not assess the protective effect of chemoprophylaxis on diarrhoeal illness. The drugs tested were effective in reducing the prevalence of infection on successive days and the proportion of infected household contacts (Table 5). This effect, however, was of short duration and after a period of 5–6 days the infection rates were similar in the treatment and control groups. The only study (*24*) that analysed the data by age groups reported that the maximum impact of chemoprophylaxis was observed in children under 5 years of age and in adults.

Only one study (*72*) has been located that tested the value of chemoprophylaxis in the prevention of diarrhoea among close contacts of cholera cases. In this trial from Bangladesh, two doses of tetracycline were administered to household contacts of hospitalized cholera cases. A similar control group was visited but did not receive any medication. All families were revisited after 10–12 days to check on any new cases of diarrhoea and hospitalization. The attack rate of diarrhoea among household contacts was similar in the treatment (13%) and control groups (14%). The occurrence of cases requiring hospitalization was, however, significantly lower in the treatment group (4%) than in the control group (8%). The presence of *V. cholerae* in the stools of contacts was not assessed.

Results from these studies suggest that chemoprophylaxis is effective in reducing the prevalence of infection among household contacts of cholera cases. This effect appears to be greatest shortly after initiation of the course and wanes rapidly so that after 5 to 6 days the infection rates are similar in the treatment and control groups. Maximum effectiveness is observed, nonetheless, during the period of greatest risk of infection. Presumably the observed effect is due to a shortening of the duration of excretion among contacts already infected and to a reduction in transmission of infection to other contacts. Khan (*72*), in contrast, found no impact of chemoprophylaxis on the attack rates of diarrhoeal illness among household contacts of cholera cases. The observed reduction in hospitalization rates for diarrhoea in the treatment group is ascribed to a possible effect on the severity of the illness. No placebo was given in Khan's study and the increased tendency to report to the hospital with diarrhoea may have been associated with the absence of medication in the control group. If the difference is real, a concomitant decrease in the attack rates of milder diarrhoea would be expected. Only a study that combines bacteriological surveillance with regular clinical assessment can clarify this issue.

Prolonged use of antimicrobials in young children. Low-dose antibiotic feeding is common practice in livestock and poultry husbandry. The addition to feed of small daily doses of broad-spectrum antibiotics has been shown to stimulate growth and to prevent infections, especially in weak animals reared in insanitary conditions or fed deficient diets (*88, 110*). The prolonged use of antimicrobials in children has been studied in a number of circumstances, such as during surveillance of recurrent attacks of rheumatic fever (*93*) or in the management of dietary deficiencies (*65*). These studies yield conflicting results, but suggest that the prolonged use of antimicrobials may occasionally be associated with improved growth and decreased morbidity and mortality, especially in malnourished children or in children suffering from a chronic disease (*122*).

Table 6. Effect of long-term chemoprophylaxis on diarrhoea morbidity in young children

Country	Study population	Age group	No. of children receiving the drug	Drug	Duration of study	Results	Reference
India	Hospitalized malnourished children	6 months to 7 years	10	Chlortetracycline or oxytetracycline	2 months	Faster recovery, reduced incidence of diarrhoea, reduced mortality.	*87*
Kenya	Hospitalized malnourished children	2 years (average)	38	Chlortetracycline	2-7 weeks	Faster weight gain, reduced incidence of intercurrent infection, reduced frequency of weight faltering or weight loss during infection, reduced duration of diarrhoea.	*89*
Honduras	Village children	6 months to 6 years	54	Iodoxychloroquinoline or metronidazole	Four 16-week periods	Reduced incidence of diarrhoea in children $\geq$ 2 years old.	*155*
USA	Children in an Apache community	1-42 months	81	Colistin sulfate	13 weeks	Children < 7 months old, increased prevalence of diarrhoea; 7-30 months old, reduced prevalence; 31-42 months old, no effect.	*60*

Table 7. Controlled trials of the chemoprophylaxis of travellers' diarrhoea

Country	Study population	Duration of trial	Drug groups	Diarrhoea attack rates (%)	Percentage reduction	Reference
Egypt and Far East	Danish tourists	25 days	Mecillinam	13	75	*15*
			Placebo	53	–	
Honduras	Peace Corps volunteers	3 weeks	Doxycycline	33	NS[a]	*132*
			Placebo	45	–	
Honduras	Peace Corps volunteers	3 weeks	Doxycycline	32	68	*131*
			Placebo	100	–	
Kenya	Peace Corps volunteers	3 weeks	Doxycycline	6	86	*129*
			Placebo	43	–	
Mexico	US students	2 weeks	Clioquinol	39	NS[a]	*67*
			Neomycin (with kaolin and pectin)	20	39	
			Placebo	34	–	
Mexico	US students	2 weeks	Neomycin	16	NS[a]	*68*
			Phthalylsulfathiazole	12	50	
			Placebo	24	–	
Mexico	US students	3 weeks	Bismuth subsalicylate	23	62	*30*
			Placebo	61	–	
Mexico	US travellers	For duration of voyage (4–13 days)	Erythromycin	0	100	*2*
			Placebo	29	–	
Mexico	US students	3 weeks	Trimethoprim-sulfamethoxazole	16	71	*31*
			Placebo	55	–	
Mexico	US students	2 weeks	Trimethoprim-sulfamethoxazole	2	94	*32*
			Trimethoprim	14	58	
			Placebo	33	–	
Mexico	US Navy personnel	For duration of exposure (0.5–2.5 days)	Doxycycline	4	81	*45*
			Placebo	21	–	
Morocco	Peace Corps volunteers	3 weeks	Doxycycline	8	83	*130*
			Placebo	46	–	
Sri Lanka[b] and Kenya	Swiss tourists	2 weeks (duration of voyage: 2–4 weeks)	Streptotriad[c]	16	58	*141*
			Placebo	38	–	
Various destinations[b]	British airline personnel and their families	3 weeks (duration of voyage: 2 days to over 6 weeks)	Streptotriad[c]	12	25	*152, 153*
			Neomycin-sulfonamides[d]	19	NS[a]	
			Placebo	16	–	

[a] No significant difference in diarrhoea attack rates compared with the control group.
[b] Poorly controlled and supervised trial.
[c] Streptomycin + sulfadimidine + sulfadiazine + sulfathiazole.
[d] Neomycin + sulfadimidine + sulfadiazine + sulfathiazole.

Four controlled trials have been located that document the effect of the prolonged administration of antimicrobials on diarrhoea morbidity in young children. They are summarized in Table 6. The first two studies, conducted in India and Kenya, report the effect of chemoprophylaxis on the recovery of children hospitalized for malnutrition (*87, 89*). Both document faster recovery and reduced incidence of diarrhoea in children receiving antibiotics. The study from Kenya also noted a decreased duration of diarrhoea. Two further studies, from Honduras (*155*) and the USA (*60*), investigated the protective effect of prolonged administration of antimicrobials on diarrhoea morbidity among children in the community. The results suggest that the prolonged administration of antimicrobials to young children in endemic areas may have an impact on diarrhoea incidence or duration in certain age groups. Detailed etiological investigations were not conducted. Also, the children were randomized within age groups to the different treatment cells and we cannot therefore assess the effect of chemoprophylaxis on the transmission of diarrhoea within households.

Chemoprophylaxis of travellers' diarrhoea. Travellers' diarrhoea may affect from 10% to 60% (*30, 125*) of travellers from low-risk to high-risk areas during their first few weeks of travel. The condition is primarily infectious, with ETEC as the most common pathogen, isolated from 30% to 70% of cases (*30, 51, 56, 97, 125, 128, 131, 135*). Fourteen controlled trials that investigated the effectiveness of chemoprophylaxis of travellers' diarrhoea are summarized in Table 7. Early studies with poorly absorbed antimicrobials, such as neomycin and phthalylsulfathiazole (*67, 68, 152, 153*), showed a modest effect. With improved understanding of the etiology of travellers' diarrhoea, doxycycline was tested in a number of trials. Sack et al. (*129, 130*) showed that a single daily dose of doxycycline was highly effective in preventing diarrhoea in Peace Corps volunteers travelling to Kenya and Morocco. Protection from ETEC and other diarrhoeas was observed during the treatment period and for the first week after cessation of doxycycline. In the Moroccan study, however, the volunteers were followed over a longer period of time and a significant increase in the attack rate was later observed in the treatment group compared with the control group. In a study in Honduras (*132*), biweekly prophylaxis with doxycycline was only marginally effective, an outcome that may be due to the decreased dosage or to the increased prevalence of resistant *Escherichia coli* found in Honduras. In a subsequent study in Honduras (*131*), a daily dose of doxycycline was found to be effective in reducing diarrhoea attack rates, although it did not prevent diarrhoea caused by doxycycline-resistant ETEC. Doxycycline also significantly reduced the severity of the illness in those who had diarrhoea. Freeman et al. (*45*) demonstrated the effectiveness of daily doxycycline in US Navy personnel making a short port call to Mexico. No rebound disease in acute diarrhoea was noted in the treatment group after departure from the high-risk area. Other antibiotics found to be effective in controlled trials are erythromycin (*2*), mecillinam (*15*), trimethoprim-sulfamethoxazole, and trimethoprim alone (*31, 32*). In the latter two studies among US students who remained in Mexico on completion of the trial, rebound diarrhoea was noted in the first week following cessation of the treatment. Finally, a non-specific drug, bismuth subsalicylate, has been found to have some protective effect when ingested in doses too large to be taken routinely (*30*).

In all of these studies, the drug was administered only for the first few weeks of residence in the high-risk area, and both effectiveness and the development of resistance during longer periods of chemoprophylaxis were not evaluated. Most studies were conducted in small groups of similar individuals, such as US students and Peace Corps volunteers, visiting a single high-risk area. These individuals were often in close contact with each other, sometimes eating together or sharing the same accommodation. Transmission of diarrhoea within the study groups may have been facilitated under such conditions. There is some evidence of this in one study (*68*). On the other hand, it is possible that the potential for transmission was reduced within the study group owing to the administration of drugs to some members of the group. No well controlled trials of chemoprophylaxis in large groups of travellers to multiple destinations have yet been carried out.

Conclusions on hypothesis 2. Numerous studies have been conducted but there is little evidence that chemoprophylaxis can reduce diarrhoea morbidity, except perhaps in travellers. No studies have been located that consider the effect on diarrhoea mortality. Chemoprophylaxis among household contacts of cholera cases has been shown to reduce the prevalence of infection during the period of most active transmission, but no impact on diarrhoea attack rates has been documented. There is some indication, however, that the severity of diarrhoea may be reduced in the treated household contacts. Broad-spectrum antibiotics administered to malnourished children have been shown to prevent nosocomial diarrhoea, but the impact of prolonged chemoprophylaxis among young children in the community remains unclear. Studies on travellers' diarrhoea indicate that chemoprophylaxis may be highly effective in reducing the incidence of diarrhoea among adult travellers making short visits to high-risk

Table 8. Reduction in cholera incidence following chemoprophylaxis of household contacts of known cholera cases

Household size (persons)	Additional case rate[a] (%)	Proportion of all cholera cases that occur as detectable index and additional cases[b] (%)	Reduction in additional case rate due to chemoprophylaxis (%)	Reduction in cholera incidence rate due to chemoprophylaxis (%)
6	5	30	20	1.2
6	5	30	40	2.4
6	5	30	60	3.6
6	5	50	20	2.0
6	5	50	40	4.0
6	5	50	60	6.0
6	15	30	20	2.6
6	15	30	40	5.1
6	15	30	60	7.7
6	15	50	20	4.3
6	15	50	40	8.6
6	15	50	60	12.8
6	25	30	20	3.3
6	25	30	40	6.7
6	25	30	60	10.0
6	25	50	20	5.6
6	25	50	40	11.1
6	25	50	60	16.7
10	5	30	20	1.9
10	5	30	40	3.7
10	5	30	60	5.6
10	5	50	20	3.1
10	5	50	40	6.2
10	5	50	60	9.3
10	15	30	20	3.4
10	15	30	40	6.9
10	15	30	60	10.3
10	15	50	20	5.7
10	15	50	40	11.4
10	15	50	60	17.2
10	25	30	20	4.2
10	25	30	40	8.3
10	25	30	60	12.5
10	25	50	20	6.9
10	25	50	40	13.8
10	25	50	60	20.8

[a] See Table 1.
[b] See Table 3.

Table 9. Reduction in shigellosis incidence following chemoprophylaxis of household contacts of known shigellosis cases

Household size (persons)	Additional case rate[a] (%)	Proportion of all shigellosis cases that occur as detectable index and additional cases[b] (%)	Reduction in additional case rate due to chemoprophylaxis (%)	Reduction in shigellosis incidence rate due to chemoprophylaxis (%)
6	20	5	20	0.5
6	20	5	40	1.0
6	20	5	60	1.5
6	20	10	20	1.0
6	20	10	40	2.0
6	20	10	60	3.0
6	30	5	20	0.6
6	30	5	40	1.2
6	30	5	60	1.8
6	30	10	20	1.2
6	30	10	40	2.4
6	30	10	60	3.6
6	40	5	20	0.7
6	40	5	40	1.3
6	40	5	60	2.0
6	40	10	20	1.3
6	40	10	40	2.7
6	40	10	60	4.0
10	20	5	20	0.6
10	20	5	40	1.3
10	20	5	60	1.9
10	20	10	20	1.3
10	20	10	40	2.6
10	20	10	60	3.9
10	30	5	20	0.7
10	30	5	40	1.5
10	30	5	60	2.2
10	30	10	20	1.5
10	30	10	40	2.9
10	30	10	60	4.4
10	40	5	20	0.8
10	40	5	40	1.6
10	40	5	60	2.3
10	40	10	20	1.6
10	40	10	40	3.1
10	40	10	60	4.7

[a] See Table 1.
[b] See Table 4.

areas if the appropriate drug is used in the correct dosage, and if the causative enteric pathogens (particularly ETEC) are susceptible. The severity of illness may also be reduced. Of concern, however, is the rebound increase in diarrhoea incidence that has been documented when travellers remain in the high-risk area after discontinuation of the drug.

Hypothesis 3. *Chemoprophylaxis in young children exposed to a recognized risk, such as contact with a known case, can reduce overall diarrhoea morbidity rates or mortality rates or severity in young children.*

The test of this hypothesis would come from a study in which chemoprophylaxis was given to young children exposed to one of the high-risk situations described in hypothesis 1, and where the impact on overall diarrhoea rates among young children was monitored. No study of this kind has been located. The two studies described in hypothesis 2, which considered the effect on diarrhoea morbidity of the prolonged administration of drugs to children in the community, cannot be used to test hypothesis 3 because the children in the treatment groups were not selected on the basis of their exposure to high-risk situations.

Hypothesis 3 must be examined, therefore, by theoretical calculations of the reductions in diarrhoea rates that may result from chemoprophylaxis of young children exposed to a recognized risk. Let us consider the most common of the identified high-risk situations: contact in the household with a known case of cholera or shigellosis, and calculate the potential impact of chemoprophylaxis on the incidence of specific diarrhoeas.[b]

The calculations for cholera are set out in Table 8. Two household sizes (6 and 10) and three additional case rates (5%, 15% and 25%) are used as before. For the purposes of this discussion, optimistic assumptions are made on the reduction in additional case rates due to chemoprophylaxis and three values (20%, 40% and 60%) are adopted on the basis of the data summarized in Table 5. The expected reduction in cholera incidence rates due to chemoprophylaxis, computed on the basis of these assumptions, ranges from 1.2% to 16.7% for a household size of 6 and from 1.9% to 20.8% for a household size of 10.

Similar calculations for shigellosis are presented in Table 9. The expected reduction in shigellosis incidence rates due to chemoprophylaxis ranges from 0.5% to 4.0% for a household size of 6 and 0.6% to 4.7% for a household size of 10.

The impact of chemoprophylaxis on overall diarrhoea incidence rates depends on the prominence of cholera and shigellosis as a cause of diarrhoea and this varies greatly from country to country. For cholera, we may take the extreme example of Bangladesh, where cholera is endemic and accounts for approximately 0.4% of all diarrhoea cases in children under 5 years (*12, 14, 92, 102, 106*). If we take values of 5–15% from Table 8 as estimates of the expected reduction in cholera incidence rates due to chemoprophylaxis of household contacts of known cholera cases, the intervention might reduce overall diarrhoea incidence rates in children under 5 years by 0.02–0.06%. In developing countries shigellosis accounts for approximately 10% of all diarrhoea cases in children under 5 years (*12, 14, 57, 64, 102*). Chemoprophylaxis of household contacts of known shigellosis cases might reduce shigellosis incidence rates by an estimated 1.5–3.5% (Table 9), and therefore might reduce overall diarrhoea incidence rates in children under 5 years by 0.15–0.35%.

In the absence of other information, it may be assumed that the reductions in cholera and shigellosis mortality rates caused by chemoprophylaxis of household contacts of known cases are the same as the reductions in incidence rates shown in Tables 8 and 9. We have calculated elsewhere (*27*) that, in Bangladesh, cholera may account for 8% of diarrhoea deaths in children under 5 years of age. If chemoprophylaxis of household contacts of known cholera cases reduces the cholera mortality rates in children under 5 years by 5–15%, then this intervention might, in Bangladesh, reduce the overall diarrhoea mortality rate in the same age group by 0.4–1.2%. Where shigellosis is responsible for 20% of diarrhoea deaths in children under 5 years (a speculative but reasonable assumption), if chemoprophylaxis of household contacts of known shigellosis cases reduces the shigellosis mortality rate in children under 5 years by 1.5–3.5%, then this intervention might reduce the overall diarrhoea mortality rate in the same age group by 0.3–0.7%.

FEASIBILITY

The likely effectiveness of chemoprophylaxis in the control of diarrhoeal diseases should not be considered in isolation from the unwanted effects of the drugs used and obstacles to the widespread implementation of the intervention.

The use of prophylactic drugs. No prophylactic drug has yet been identified which is universally safe and effective. A number of drugs, such as neomycin (*63, 69*) and the halogenated hydroxyquinolines (*109, 114, 133*), previously in common use, are now out of

[b] The formula used to make these calculations is available on request from R.G.F.

favour because of their potential adverse reactions. Antimicrobials are popular, but they have selective action against certain bacteria and protozoa only. A number of other agents, such as phage preparations (*82, 107, 112*), lactobacilli preparations (*21, 26*), and bismuth subsalicylate (*30, 53*) have been considered for the chemoprophylaxis of diarrhoea but are probably of limited value.

Antimicrobials are all associated with adverse reactions, some of them severe, and their use may be contraindicated in certain persons; for example, the administration of tetracyclines to children and to pregnant or lactating women is discouraged because of their dental staining effect (*156*). Antimicrobials may also increase host susceptibility to some enteric pathogens (*16, 96*), and alter the activity of pancreatic enzymes (*17*) and the metabolism of bile acids (*58*). Of greatest concern, however, is that the use of antimicrobials provides an advantage to resistant strains and imposes selective pressure to assist in their spread (*36, 85, 101, 108, 142, 162*). There is also the sinister possibility that the emergence of resistance is associated with increased virulence or communicability of certain strains (*33, 117, 137, 143, 165*). Finally, antimicrobials may mask other bacterial infections and complicate their therapy. Their extensive use cannot be recommended in the absence of monitoring for adverse reactions.

Implementation. The application of chemoprophylaxis among family contacts of known cholera and shigellosis cases requires the correct identification of the index cases followed by the administration of drugs to their family contacts. Under normal circumstances, only hospitalized diarrhoea cases are likely to be investigated and correctly diagnosed. As discussed earlier, hospitalization rates vary widely from area to area and will often be lower than those adopted in our calculations. Outbreaks of diarrhoeal disease that need intensified control measures should be detected as soon as possible, but reporting systems based on routine data collected from health facilities are not very sensitive (*54*) and the laboratory services needed to make an accurate diagnosis of etiology and to test for antimicrobial sensitivity may not always be available (*47, 94*). Once the index case of cholera or shigellosis is recognized, the at-risk family members must be located for the distribution of drugs. Time is at a premium here, as the additional case rate among household contacts is highest on the first day of observation in the studies reported in Table 1 and falls rapidly thereafter. The distribution of drugs may be a complex task, especially in rural areas and when a multiple-dose drug regimen is used.

In short, the detection of cases and the rapid follow-up of their contacts and distribution of drugs require skills and resources that are scarce in developing countries. The workload may be especially heavy in epidemic situations when the number of contacts to be reached will be very high. Chemoprophylaxis might then direct attention from other, more effective, control measures.

COST

The costs of chemoprophylaxis have not been documented. The costs involved fall into four main categories:

— The cost of the drugs. Drug bills place a considerable burden on the health budget of most governments. There are large cost variations between drugs and even for the same drug, depending on the price per unit for that particular drug, the quantity required, the preparation chosen, and the purchasing and distribution systems used.

— The cost of surveillance (including laboratory surveillance). This cost is difficult to determine as few reporting systems for health expenditure list these items separately. This cost would be shared with other interventions.

— The cost of the distribution of the drugs, including manpower and logistics.

— The cost of unwanted effects. These include the cost of treatment of adverse reactions due to the drugs used in chemoprophylaxis and the increased cost of new drugs used in therapy to replace old ones that become inadequate because of the emergence of antimicrobial resistance.

CONCLUSIONS

There is little evidence that chemoprophylaxis is effective in reducing diarrhoea morbidity and mortality. The most common application of chemoprophylaxis in developing countries is to prevent cholera or shigellosis among selected high-risk groups, such as household contacts of known cases. A theoretical case has been made out, based on optimistic assumptions, that chemoprophylaxis of household contacts of known cholera cases in Bangladesh might reduce overall diarrhoea incidence rates in children under 5 years of age by 0.02–0.06% and diarrhoea mortality rates by 0.4–1.2%. Chemoprophylaxis of household contacts of known shigellosis cases might reduce diarrhoea incidence rates by 0.15–0.35% and diarrhoea mortality rates by 0.3–0.7% in the same age group.

The correct identification of index cases of cholera and shigellosis, followed by the rapid distribution of drugs to their household contacts, requires skills and resources that are scarce in the developing countries.

All the drugs currently used have side-effects that should be carefully monitored. Chemoprophylaxis can contribute to the widespread emergence and dissemination of antimicrobial resistance. The costs of chemoprophylaxis have not been documented but are likely to be high and no long-term benefits may be derived. The available evidence suggests, therefore, that chemoprophylaxis is not feasible in many settings and that, even if successfully implemented, it is not a cost-effective intervention for national diarrhoeal disease control programmes.

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RÉSUMÉ

INTERVENTIONS DESTINÉES À LA LUTTE CONTRE LES MALADIES DIARRHÉIQUES CHEZ LES JEUNES ENFANTS: CHIMIOPROPHYLAXIE

Cet article est le sixième d'une série passant en revue les interventions possibles en vue de réduire la morbidité et la mortalité par diarrhée parmi les enfants de moins de 5 ans dans les pays en développement. Un certain nombre de situations font courir aux jeunes enfants un risque accru de diarrhée. Parmi celles-ci la mieux étudiée dans les pays en développement est le contact avec un cas connu dans la famille ou le ménage. L'application la plus fréquente de la chimioprophylaxie dans ces pays vise à prévenir le choléra ou les shigelloses parmi les contacts de cas connus dans les ménages. Il ne semble pas que la chimioprophylaxie puisse réduire efficacement la morbidité et la mortalité par diarrhée, sauf peut-être chez les voyageurs. D'après les calculs théoriques du présent article (fondés sur des hypothèses optimistes), la chimioprophylaxie appliquée à des contacts dans les ménages comptant des cas connus, au Bangladesh, pourrait réduire de 0,02–0,06% les taux d'incidence globaux de la diarrhée et de 0,4–1,2% les taux de mortalité par diarrhée chez les enfants de moins de 5 ans. En ce qui concerne les shigelloses, la chimioprophylaxie administrée à des contacts de cas connus dans des ménages pourrait réduire de 0,15–0,35% les taux d'incidence globaux de la diarrhée et de 0,3–0,7% les taux de mortalité par diarrhée dans le même groupe d'âge.

Le dépistage correct des cas initiaux de choléra et de shigellose suivi d'une distribution rapide de médicaments à leurs contacts dans les ménages demande des compétences et des ressources qui sont rares dans les pays en développement. Tous les médicaments actuellement en usage présentent des effets secondaires qui doivent être minutieusement surveillés. En outre, point capital, la chimioprophylaxie peut contribuer à l'apparition et à la dissémination de la résistance aux antimicrobiens sur une grande échelle. On ne connaît pas les coûts de la chimioprophylaxie, mais ils sont probablement élevés et l'on ne peut en attendre d'avantages à long terme. D'après les données existantes, la chimioprophylaxie est donc irréalisable dans de nombreuses circonstances et, même si elle est appliquée avec succès, ce n'est pas une intervention rentable pour les programmes nationaux de lutte contre les maladies diarrhéiques.

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Interventions for the control of diarrhoeal diseases among young children: improving water supplies and excreta disposal facilities*

S. A. ESREY,[1] R. G. FEACHEM,[2] & J. M. HUGHES[3]

A theoretical model is proposed that relates the level of ingestion of diarrhoea-causing pathogens to the frequency of diarrhoea in the community. The implications of this model are that, in poor communities with inadequate water supply and excreta disposal, reducing the level of enteric pathogen ingestion by a given amount will have a greater impact on diarrhoea mortality rates than on morbidity rates, a greater impact on the incidence rate of severe diarrhoea than on that of mild diarrhoea, and a greater impact on diarrhoea caused by pathogens having high infectious doses than on diarrhoea caused by pathogens of a low infectious dose. The impact of water supply and sanitation on diarrhoea, related infections, nutritional status, and mortality is analysed by reviewing 67 studies from 28 countries. The median reductions in diarrhoea morbidity rates are 22% from all studies and 27% from a few better-designed studies. All studies of the impact on total mortality rates show a median reduction of 21%, while the few better-designed studies give a median reduction of 30%. Improvements in water quality have less of an impact than improvements in water availability or excreta disposal.

Of the several interventions that may reduce diarrhoea morbidity and mortality rates (*38*), the improvement of water supply and excreta disposal facilities has attracted particular interest. These environmental improvements, together with improvements in living standards, played a major role in reducing diarrhoea rates and controlling epidemic typhoid and cholera in Europe and North America between 1860 and 1920. It is anticipated that the improvement of water supply and excreta disposal in poor communities in developing countries today will have a substantial impact on diarrhoea morbidity and mortality rates in those communities. This expectation provides part of the motivation for the International Drinking Water Supply and Sanitation Decade (1981-1990), the aims of which are to increase the rate at which new water supply and excreta disposal facilities are constructed and to maximize the probability that they will be correctly operated, maintained and used.

The potential impacts of improved water supply and excreta disposal on diarrhoea and other water-related diseases in developing countries have been discussed and debated at length over the past decade. White et al. (*86*) provided a conceptual framework for the debate in the context of studies in East Africa; McJunkin (*56*) reviewed the topic extensively; Saunders & Warford (*70*) summarized the water supply impact studies; Feachem et al. (*39*) summarized the excreta disposal impact studies; and Blum & Feachem (*13*) and Esrey & Habicht (*28*) considered the methodological difficulties inherent in attempts to measure the impact of water supply and excreta disposal projects on diarrhoea.

In this review we analyse the effectiveness of water supply and excreta disposal improvements for reducing diarrhoea rates in young children in developing countries. We also examine their impact on diarrhoea-related infections, nutritional status, and mortality. We make no attempt to analyse other impacts of water supply and excreta disposal improvements or to compute an overall cost-benefit ratio for these investments. This paper is the ninth in a series of reviews of potential anti-diarrhoea interventions (*2, 25, 26, 32, 34-36, 38*).[a]

* Requests for reprints should be sent to the Director, Diarrhoeal Diseases Control Programme, World Health Organization, 1211 Geneva 27, Switzerland.

[1] Division of Nutritional Sciences, Cornell University, Ithaca, New York 14853, USA.

[2] Head, Department of Tropical Hygiene, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, England.

[3] Director, Hospital Infections Program, Center for Infectious Diseases, Centers for Disease Control, Public Health Service, US Department of Health and Human Services, Atlanta, GA 30333, USA.

[a] ASHWORTH, A. & FEACHEM, R. G. *Interventions for the control of diarrhoeal diseases among young children: improving lactation*. Unpublished WHO document CDD/85.2, 1985.

EFFECTIVENESS

For improved water supply or excreta disposal facilities to be an effective diarrhoea control intervention, it must be true that:

either

water supply or excreta disposal improvements can reduce the ingestion by young children of pathogens causing diarrhoea	*hypothesis 1*

and

a reduction in the ingestion of these pathogens by young children can reduce diarrhoea morbidity or mortality rates	*hypothesis 2*

or

water supply or excreta disposal improvements can reduce diarrhoea morbidity or mortality rates among young children	*hypothesis 3*

The effectiveness of improved water supply and excreta disposal would be suggested by a demonstration either of the correctness of hypotheses 1 and 2 or the correctness of hypothesis 3. In some other reviews in this series (for instance, *35, 36*), most of the literature bears on hypotheses 1 and 2, and hypothesis 3 must be handled by theoretical calculations. Here the reverse is the case: there are few data on hypotheses 1 and 2 and an extensive literature on hypothesis 3. The evidence for and against the three hypotheses is examined below.

Hypothesis 1. *Water supply or excreta disposal improvements can reduce the ingestion by young children of pathogens causing diarrhoea.*

There is some evidence to suggest that three types of water and excreta disposal improvements (improved water quality, increased water availability and quantity associated with better hygiene practices, and improved excreta disposal facilities) may reduce the ingestion of pathogens causing diarrhoea (*33*).

All the major infectious agents of diarrhoea are transmitted by the faecal-oral route, and all can be transmitted via contaminated water. For most agents water-borne transmission has been documented. For some agents there is good evidence that, at least in some places at some times, water is a major vehicle of transmission. Notable examples are *Salmonella typhi, Vibrio cholerae*, and *Giardia lamblia* (*39*). Traditional water sources are often highly contaminated with faecal matter. Improved water sources may be free of contamination or considerably less contaminated than unimproved water sources (*30, 77*). Uncontaminated source water may become polluted by the time it is ingested, and water storage in home containers may result in increased contamination depending on storage conditions (*37, 66, 72*).

Increased water availability and quantity, associated with improved hygiene, may reduce faecal contamination of the hands. Proper cleaning of utensils, food, and home environments is also likely to reduce transmission of faecal matter. The transmission of all the main diarrhoea-causing agents is probably influenced to some degree by increased water availability and quantity, but it is *Shigella* transmission that has been particularly associated with poor personal and domestic hygiene (*45, 78*). This may be because of the low infectious dose of *Shigella* relative to other bacterial enteric pathogens, or it may be only because *Shigella* has been most studied. The relationship between personal hygiene and the newly-recognized diarrhoea agents (especially *Campylobacter jejuni*, enterotoxigenic *Escherichia coli*, and rotavirus) should be studied.

All the major infectious agents of diarrhoea are shed by infected persons via the faeces, and therefore hygienic disposal of human excreta plays a role in controlling them. Use of toilets by all members of the community should reduce faecal contamination of houses, yards and gardens, and the neighbourhood. In addition, proper treatment and disposal of human excreta would prevent faecal contamination of fields, crops, and receiving water-bodies, which would in turn further reduce the transmission of faecal pathogens. The hygienic disposal of the faeces of children too young to use the toilet is of the utmost importance, because such children constitute an important reservoir of several agents of diarrhoea (for instance, rotavirus and enterotoxigenic *E. coli*).

Hypothesis 2. *A reduction in the ingestion of these pathogens by young children can reduce diarrhoea morbidity or mortality rates.*

The ingested dose of a pathogen required to cause diarrhoea depends upon the particular properties of the pathogen and upon a number of host factors. The general relationship between ingested dose and proportion of exposed persons contracting diarrhoea

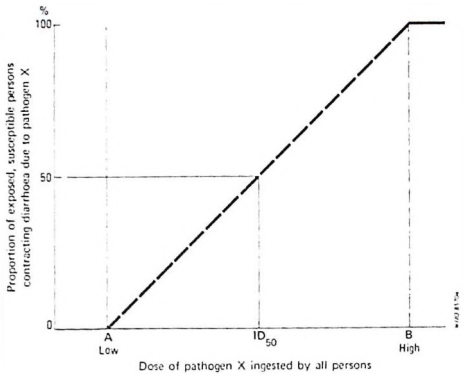

Fig. 1. Dose–response relationship for a group of susceptible persons, all exposed to an equal dose of pathogen X.

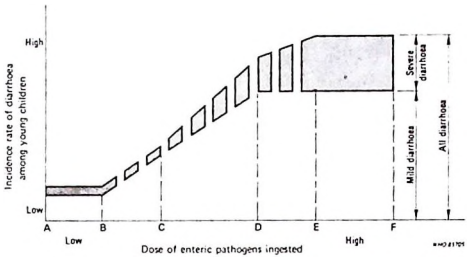

Fig. 2. Dose–response relationship for young children under various levels of exposure to an array of enteric pathogens.

is shown in Fig. 1. In the dose range below A, no one becomes ill.[b] In the dose range above B, all susceptible persons develop diarrhoea. Between A and B lies an intermediate range in which some persons become ill and others do not. The dose at which 50% of challenged persons become ill is known as the median infectious dose (ID_{50}), which is the figure generally reported from volunteer studies. Little is known about the shape of the curve in the intermediate range and, for this reason, a broken line is shown in Fig. 1. Both the shape of the curve and the values of A, B, and the ID_{50} depend upon the particular pathogen, its method of ingestion (in water or in food), and a variety of features of the exposed group of people, such as age and immunity.

Available ID_{50} and other infectious dose data have been recently reviewed for all the major diarrhoea-causing pathogens (*39*). For bacterial agents there is a wide range of ID_{50} values—from around 10^3 for *Shigella* to 10^8–10^{11} for *Vibrio cholerae*. Less is known about the viral and protozoal agents of diarrhoea, although there are grounds for assuming that the ID_{50} values are relatively low ($< 10^2$). Nearly all infectious dose data are derived from studies on volunteers in which the subjects were healthy adults from developed countries. The doses necessary to infect children, particularly malnourished children, may be very different. ID_{50} values also depend on the food or drink with which the pathogens are ingested; therefore, they may differ among countries with differing dietary and child-feeding practices. In addition, in situations where large numbers of persons are exposed to diarrhoea-causing pathogens, the ID_1 or $ID_{0.1}$ values may be of greater epidemiological relevance than the ID_{50} values. More reliance can be placed on the relative ranking of pathogens by ID_{50} than on the absolute dose values obtained from studies on volunteers.

The relationship depicted in Fig. 1 may be generalized to a group of young children having different levels of water supply and excreta disposal services and, consequently, different levels of ingestion of enteric pathogens (Fig. 2). Consider first the incidence rate of mild diarrhoea. At low levels of ingestion (A–B), there remains an appreciable incidence of mild diarrhoea, made up of an irreducible minimum of infectious diarrhoea, plus diarrhoea not due to enteric pathogens. This situation is exemplified by children in wealthy communities in developed countries. When ingestion rises above point B, the incidence rate of mild diarrhoea also rises. At point D saturation is reached, and further increases in the ingestion of pathogens do not result in an increased incidence rate of mild diarrhoea. As in Fig. 1, the shape of the curve between points B and D on the "mild diarrhoea incidence" line in Fig. 2 is unknown, so a broken line is shown. Poor communities in developed and developing countries, with their elevated diarrhoea incidence rates, clearly lie to the right of point B.

The incidence rate of severe diarrhoea, which may be defined by stooling rate, stool volume, duration, degree of dehydration or other measures, is indicated on Fig. 2 by the distance between the two lines (the shaded band). The incidence rate of severe diarrhoea is less than that of mild diarrhoea, but it represents an increasing proportion of the total diarrhoea incidence rate as the ingestion of enteric pathogens rises above

[b] Despite the representation in Fig. 1, it may be that for some pathogens A = 0.

the level represented by point C.[c] The incidence rate of severe diarrhoea is shown in Fig. 2 to be constant in the range A–C, to rise in the range C–E, and to be constant in the range E–F. The breakpoints for severe diarrhoea incidence rate (C and E) are offset to the right of the equivalent points for mild diarrhoea incidence rate (B and D), on the assumption that for a single pathogen a higher ingested dose is necessary to produce severe diarrhoea than mild diarrhoea. There is direct experimental confirmation of this for enterotoxigenic *E. coli* (*27*) and for *Vibrio cholerae* (*19*). Indirect evidence is also available for *Salmonella*, for which there is an inverse relationship between dose and incubation period (*12*) and an inverse relationship between incubation period and severity (*10*). Fig. 2 assumes that the ID_{50} for severe symptoms is higher than the ID_{50} for mild symptoms for most enteric pathogens.

The model put forward in Fig. 2 is tentative and grossly simplified. It may be more applicable to young children than to a whole community. The complex role of immunity is not specifically addressed in the model and, for certain pathogens, the improvement of hygienic conditions may lead to an increase in diarrhoea incidence rates in older age groups. A more complete modelling of the interrelationships between hygiene levels and diarrhoea incidence is difficult because of the wide differences in epidemiology and immunology among the major diarrhoea-causing agents. This simplified model provides some theoretical basis for the explanation of a number of observed features of childhood diarrhoea. We hope that it may stimulate others to conduct studies to define more precisely the complex reality.

The implications of Fig. 2 for diarrhoea control by reducing pathogen ingestion are as follows. If pathogen ingestion is reduced within the range F–E, the incidence rates of mild or severe diarrhoea may not change. In the range E–D, severe diarrhoea rates may fall, but mild diarrhoea rates may not. Because severe cases usually represent a small proportion of all cases, surveillance of all cases may fail to detect a fall in incidence rate in this range. For instance, if a water supply and excreta disposal project reduced the dose of ingested pathogens from E to D, Fig. 2 suggests that the incidence rate of severe diarrhoea might fall by about 44% but the incidence rate of all diarrhoea by only about 12%. Many diarrhoeal disease studies are unable to detect a 12% fall in total incidence rate or to show it to be statistically significant. In the range D–E an impact is more likely to be documented if data on the incidence rate of severe diarrhoea (however defined) are collected. Measures of diarrhoea or total mortality are also more likely to detect an impact in this range (see below).

In the range D–C in Fig. 2, both mild and severe diarrhoea incidence rates are falling, and a change may be detected by surveillance of all cases. Severity, child growth, or mortality parameters are also likely to change in this range. In the range C–B, only the incidence rate of mild cases is declining but, since most cases are mild, surveillance of all cases may detect an impact. In the range B–A, reductions in pathogen ingestion have no effect on diarrhoea of any type.

This discussion of the implications of the model presented in Fig. 2 may be restated in two other ways. First, since it is severe episodes that lead in some instances to death, the mild diarrhoea incidence rate in Fig. 2 may be replaced by the total diarrhoea incidence rate and the severe diarrhoea incidence rate by the diarrhoea mortality rate. Diarrhoea mortality rates may therefore be a more responsive indicator in the range D–E or ranges overlapping with the range D–E than diarrhoea morbidity rates. Diarrhoea mortality rates will not, however, be a good measure of impact in areas where oral rehydration therapy is widely available and averts most deaths from dehydration. Second, since there are putative differences in ID_{50} values, not only between degrees of severity of diarrhoea caused by a single pathogen, but also among different pathogens, the mild diarrhoea incidence rate may be replaced by the incidence rate of etiologies having low ID_{50} values, and the severe diarrhoea incidence rate by the incidence rate of etiologies having high ID_{50} values.[d] This model is consistent with known facts, in that developed countries, which may lie in the range A–C, have a small proportion of cholera and enterotoxigenic *E. coli* diarrhoea (high ID_{50}), a high proportion of rotavirus diarrhoea (low ID_{50}), and an intermediate proportion of shigellosis (intermediate ID_{50}).[e]

It must be emphasized that the model presented in Fig. 2 is hypothetical and grossly simplified. It is, however, consistent with several established facts and, as discussed below, it is helpful in explaining some of the variation in the recorded impacts of water supply and excreta disposal projects on diarrhoeal diseases. A somewhat similar model has been previously published (*73*).

[c] The highest ratios of severe diarrhoea to all diarrhoea have been recorded in some epidemics, which may be associated with exceptionally high average doses of pathogens ingested by an exposed population.

[d] It is not implied here that pathogens having relatively low ID_{50} values cause relatively mild diarrhoea and vice versa. This is clearly untrue in the cases of rotavirus and *Shigella*, both of which have relatively low ID_{50} values but cause relatively severe diarrhoea.

[e] This analysis probably only applies to the anthroponotic agents mentioned here. For the zoonotic diarrhoea agents, such as *Salmonella* and *Campylobacter*, most transmission in developed countries is from infected animals to man via contaminated food products, and so levels of pathogen ingestion depend more on farming methods, food handling practices, and diet than on domestic water supply and human excreta disposal facilities.

Hypothesis 3. *Water supply or excreta disposal improvements can reduce diarrhoea morbidity or mortality rates among young children.*

Numerous attempts have been made to measure the impact on health of improved water supply or sanitation. We selected for review those 67 studies from 28 countries[f] that measured health impact in terms of diarrhoea morbidity, *Shigella* infection or disease, cholera, *Entamoeba histolytica* infection, *Giardia lamblia* infection, nutritional anthropometry, diarrhoea mortality, or total mortality. These studies are grouped in Table 1 according to the health impact indicator measured and ordered alphabetically by country within each group.

The data abstracted from the studies listed in Table 1 are summarized in Tables 2-5. All the studies in Table 1 display methodological deficiencies (*13*, *28*) although some studies were better than others. The total number of studies is large (67), but only a few are reported in sufficient detail to allow an objective assessment of their methodological and analytical

[f] Studies were identified from previous reviews, supplemental enquiries to workers in the field, computer searches in five languages, and from unpublished papers presented at the International Seminar on Measuring the Health Impact of Water and Sanitation Programmes, Cox's Bazaar, Bangladesh, 21-25 November 1983 (sponsored by the International Centre for Diarrhoeal Diseases Research, Bangladesh, and the Ross Institute, London).

Table 1. Studies on the impact of water supply or excreta disposal on diarrhoea morbidity and mortality, enteric infections, total mortality, and nutritional status reviewed in this paper

Indicator	Country	Reference
Diarrhoea morbidity	Bangladesh	*22, 54, 74,*[a]
	Chile	*24*
	Colombia	*51, 88*
	Costa Rica	*62*
	Egypt	*82*
	Ethiopia	*40*
	Gambia	See below[b]
	Guatemala	*16, 72*
	Haiti	*79*
	India	*53, 66, 67, 81*
	Iran (Islamic Rep. of)	*82*
	Kenya	*86,*[c]
	Lesotho	*37*
	Mozambique	See below[d]
	Sri Lanka	*82*
	Saint Lucia	*44,*[e]
	Sudan	*6, 82*
	United Kingdom	*17*
	USA	*8, 15, 55, 64, 69, 71, 84*
	Venezuela	*82, 87*
	Zambia	*4*
Cholera	Bangladesh	*22, 46, 49, 50, 54, 76, 77*
	Philippines	*3*
Entamoeba histolytica infection	Costa Rica	*62*
	Egypt	*20*
	India	*59, 66*
	Kenya	See below[c]
	Libyan Arab Jamahiriya	*41*
	USA	*15, 29, 57*

Table 1: *continued on next page*

Table 1: *continued*

Indicator	Country	Reference
Giardia lamblia infection	Costa Rica	*62*
	Egypt	*20*
	India	*66*
	Kenya	See below[c]
	Libyan Arab Jamahiriya	*41*
	USA	*29*
Shigella infection or disease	Bangladesh	*22, 48, 65*[a]
	Costa Rica	*62*
	Egypt	*82*
	Guatemala	*7*
	India	*66*
	Iran (Islamic Rep. of)	*82*
	Libyan Arab Jamahiriya	*41*
	Panama	*52*
	Sri Lanka	*82*
	Sudan	*82*
	USA	*45, 55, 71, 78, 84*
	Venezuela	*82*
Nutritional status	Bangladesh	See below[e]
	Colombia	*21*
	Fiji	See below[f]
	Nigeria	*80*
	Philippines	See below[j]
	Saint Lucia	See below[k]
Diarrhoea mortality	Brazil	*83*
	India	*89*
Total mortality	Brazil	*61*
	Costa Rica	*43*
	Egypt	*85*
	Guatemala	*1*
	Malaysia	*18*
	Sri Lanka	*60, 63*
	Sudan	*6*

[a] RAHAMAN, M. M. *The Teknaf Health Impact Study: methods and results*. Paper presented at the International Workshop on Measuring the Health Impacts of Water Supply and Sanitation Programmes, Cox's Bazaar, Bangladesh, 21–25 November 1983.

[b] PICKERING, H. *The role of anthropologists in studying diarrhoea epidemiology: a case study from The Gambia*. Paper presented at the International Workshop on Measuring the Health Impacts of Water and Sanitation Programmes, Cox's Bazaar, Bangladesh, 21–25 November 1983.

[c] FENWICK, K. W. H. The short-term effects of a pilot environmental health project in rural Africa: the Zaina scheme re-assessed after four years. (undated manuscript).

[d] CAIRNCROSS, S. & CLIFF, J. *Water and health in Mueda, Mozambique*. Paper presented at the International Workshop on Measuring the Health Impacts of Water and Sanitation Programmes, Cox's Bazaar, Bangladesh, 21–25 November 1983.

[e] YEE, V. S. *Household level correlates of child nutritional status in Fiji*. MPS thesis. Division of Nutritional Sciences, Cornell University, Ithaca, New York, 1984.

[f] MAGNANI, R. J. & TOURKIN, S. C. *Impact of improved urban water supplies in the Philippines: methods and results*. Paper presented at the International Workshop on Measuring the Health Impacts of Water and Sanitation Programmes, Cox's Bazaar, Bangladesh, 21–25 November 1983.

[g] HENRY, F. J. *Health impact of water and sanitation interventions in St. Lucia*. Paper presented at the International Workshop on Measuring the Health Impacts of Water Supply and Sanitation Programmes, Cox's Bazaar, Bangladesh, 21–25 November 1983.

Table 3. Percentage reductions in diarrhoea morbidity rates attributed to water supply or excreta disposal improvements by adult literacy rate of the country and magnitude of service improvement

Adult literacy rate[a] (%)	Small service improvements[b]		Large service improvements[b]	
	No. of results	Median (%)	No. of results	Median (%)
< 40	11	18	7	46
40–75	4	20	8	39
> 75	10	16	13	32

[a] Data on adult literacy, by country, from *World development report, 1983* (Washington, World Bank).

[b] See footnote *g*, page 762.

to small service-level improvements (Table 3). If a large service-level improvement is made, the percentage reduction in diarrhoea morbidity rates achieved is inversely related to the pre-intervention level of hygiene (Table 3). The greatest impact is achieved when the pre-intervention hygiene level is worst. For small improvements in service level, impacts appear less dependent upon the pre-intervention hygiene level. These conclusions are consistent with the hypothetical model depicted in Fig. 2 and suggest that the impact of water and sanitation improvements depends in part on the presence and interaction of other risk factors.

Impact on specific infections. When impact on total diarrhoea morbidity is broken down by etiology, it is likely, as discussed above, that different specific diarrhoeas will be reduced by different amounts. Table 4 presents data on impacts on cholera, *Shigella* infection or disease, and infection by *Ent. histolytica* and *G. lamblia*. Since the distinction between the severe and mild diarrhoea bands in Fig. 2 is merely one of infectious dose (ID), in ranges including D–E, any reduction in pathogen ingestion will produce a greater percentage reduction in the incidence rate of the high ID etiologies than the low ID etiologies. Thus the impact of a water supply and excreta disposal improvement (in ranges including D–E) on specific etiologies may be in the following descending order of magnitude: cholera, enterotoxigenic *E. coli*, *Shigella*, the protozoa, rotavirus. The relative impacts on *Shigella* and the protozoa are supported by the data in Table 4. The anomalous cholera data are discussed elsewhere (*31*).

Data on the impact of water supply and excreta disposal projects on enterotoxigenic *E. coli* and rotavirus incidences are not yet available, but it is anticipated that the impact on enterotoxigenic *E. coli* will be considerable and on rotavirus negligible. The latter prediction is indirectly supported by data showing that the incidence rate of rotavirus diarrhoea among children under 2 years of age is 0.3–0.4 episodes per child per year in both Bangladesh (*11*) and Winnipeg, Canada (*42*).

Impact on nutritional anthropometry. If water supply and excreta disposal improvements reduce diarrhoea incidence rates or duration among young children, then nutritional anthropometric indicators should also improve because of the inverse relationship between time spent with diarrhoea and child growth (*58, 68*). Six studies that investigated the relationship between water supply or excreta disposal improvements and nutritional status are summarized in Table 5. All six studies reported an association between improved water supply or excreta disposal and improved nutritional status. In two studies, in Fiji and the Philippines, attempts to control for extraneous risk factors reduced the differences between the control and intervention groups, but some of these differences were nonetheless found to be statistically significant.

Impact on mortality. Only two studies were located that reported the impact of water supply or excreta disposal improvements on diarrhoea mortality rates (Table 1); a 41% median reduction in diarrhoea mortality rate was calculated from them. Both studies were concerned with the impact of improved water supplies in urban areas, and in neither was the study method well described. A further eight studies reported impacts of water supply or excreta disposal improvements on mortality from all causes (Table 1), and they indicated a 21% (range, 0–81%) median reduction in mortality rate.

Table 4. Percentage reductions in morbidity or infection rates of cholera, *Shigella, Entamoeba histolytica*, and *Giardia lamblia* attributed to water supply or excreta disposal improvements

Disease or infection	No. of results	Percentage reduction	
		Median (%)	Range (%)
Cholera	11	41	0–91
Shigella	27	48	0–81
Entamoeba histolytica	17	2	0–80
Giardia lamblia	10	0	0–20

Table 5. Improvements in nutritional status attributed to various types of water supply or excreta disposal improvement

Country	Nutritional indicator[a]	Age (months)	Type of intervention[b]	Value of indicator: Control group	Value of indicator: Target group	Reference
Bangladesh	Percentage with H/A > 90% of standard	0–11	Q + A + E	75	76	See below[d]
		12–23	Q + A + E	50	51	
		24–35	Q + A + E	45	48	
	Percentage with W/A > 75% of standard	0–11	Q + A + E	59	63	
		12–23	Q + A + E	44	43	
		24–35	Q + A + E	47	50	
Colombia	Percentage with W/A > 90% of standard	6–30	E	26	47	*21*
		6–30	A	22	51	
	Percentage with H/A > 95% of standard	6–30	E	26	48	
		6–30	A	20	53	
Fiji	Mean percentage of:					See below[e]
	standard W/A					
	urban	0–59	E	102	100	
	rural	0–59	E	95	102	
	standard H/A					
	urban	0–59	E	100	100	
	rural	0–59	E	99	103	
Nigeria	Percentage with:					*80*
	W/A > 75% of standard	6–59	A	50	69	
	H/A > 90% of standard	6–59	A	80	69	
	W/H > 80% of standard	6–59	A	63	90	
Philippines	Percentage with W/A > 75% of standard					See below[f]
	pre-intervention	6–54		74	75	
	post-intervention	6–54	Q + A	71	80	
Saint Lucia	Percentage with W/A > 90% of standard	1–3	A (A + E)	93	92 (86)[c]	See below[g]
		4–6		72	90 (88)	
		7–9		51	78 (76)	
		10–12		44	76 (73)	
		13–15		50	76 (58)	
		16–18		51	74 (57)	
		19–21		53	75 (66)	
		22–24		54	79 (71)	

[a] W/A = weight for age; W/H = weight for height; H/A = height for age.

[b] Q = water quality improvement, A = water availability improvement, E = excreta disposal improvement.

[c] Figures not in parentheses refer to the communities receiving water availability improvements (A). Figures in parentheses refer to communities receiving water availability improvements plus excreta disposal facilities (A + E).

[d] See footnote *a* to Table 1.

[e] See footnote *e* to Table 1.

[f] See footnote *f* to Table 1.

[g] See footnote *g* to Table 1.

Fig. 2 predicts a larger impact on diarrhoea mortality than morbidity over a wide range of conditions. The impact on total mortality will depend on the proportion of all mortality that is due to diarrhoea and the degree to which water supply and excreta disposal improvements affect the causes of death other than diarrhoea. Since water supply and excreta disposal improvements will have little impact on some major causes of death (for instance, respiratory infection, measles, malaria, and neonatal tetanus), it is to be expected that the impact on diarrhoea mortality is considerably greater than the impact on all mortality.

Results from selected studies. For the analyses so far, we have used pooled data from all studies listed in Table 1 to give an overview of all documented experiences on the impacts of water supply and excreta disposal improvements on diarrhoea. It is instructive to compare these findings with the results of a few of the better studies. Criteria for judging the quality of each study have been developed and are reported elsewhere (*28*).

The first finding from this selective analysis was that all studies that reported a negative impact were flawed in one or more major respects. In other words, the better studies consistently reported positive impacts.

The best studies were on total mortality (*18, 43, 60*), and the median impact on total mortality rates reported from these studies was a reduction of 30%. Analysis for statistical interactions revealed a range of reductions in mortality rates of 8–64%, depending on the type of intervention and on the presence of other risk factors, such as poor feeding practices and low literacy rates. For example, in one study (*18*) excreta disposal improvements were reported to have a larger impact on infant mortality rates than water supply, but the magnitudes of these impacts were greatly affected by whether the infants were breast-fed. The impact of the environmental interventions was greater for non-breast-fed infants than for breast-fed infants. Thus, it is likely that non-breast-fed infants were further to the right along the horizontal axis in Fig. 2 than were breast-fed infants. Another study reported that excreta disposal improvements had a greater impact on mortality in families with literate mothers than in families with illiterate mothers (*60*). This may reflect an increased ability of literate mothers to make correct use of the new excreta disposal facilities.

Two studies on nutritional status also examined statistical interactions. In one,[h] excreta disposal was reported to have more impact in rural than in urban areas. In the other,[i] water quality improvements had an impact only among higher income households.

Studies on diarrhoea morbidity were not as well controlled as the mortality studies referred to above. A median reduction in diarrhoea morbidity rates of 27% (range, 0–68%) was found in the studies judged to be most satisfactory (*40, 51, 55, 71*).[j, k, l]

This brief review of selected studies of superior design leads to two conclusions. First, the median reductions in diarrhoea morbidity rates (27%) and total mortality rates (30%) are a little higher than the values found by analysing all studies. Second, the magnitude of the impact depends greatly on the presence of other risk factors. More knowledge of these interactions would enable the appropriate type of intervention to be targeted to families that are likely to benefit the most.

FEASIBILITY

Nearly all developing countries are currently engaged in substantial programmes to improve water supplies in both rural and urban areas. The urban programmes date back, in many cases, to the 1920s or earlier, while many of the rural programmes were initiated in the 1960s. This considerable experience in water supply programmes throughout the world has been copiously documented (e.g., *23*) and is continuously monitored by WHO.[m] Improved water supplies can be provided to almost all people in all developing countries, and the technologies for achieving this are, for the most part, well established. Several problems remain, however, such as poor operation and maintenance, inappropriate choice of technology, inadequate revenue collection, failure to sustain community participation, and high rates of water leakage and wastage.

All countries have experience in excreta disposal

[h] YEE, V. S. *Household level correlates of child nutritional status in Fiji*. MPS thesis. Division of Nutritional Sciences, Cornell University, Ithaca, New York, 1984.

[i] MAGNANI, R. J. & TOURKIN, S. C. *Impact of improved urban water supplies in the Philippines: methods and results*. Paper presented at the International Workshop on Measuring the Health Impacts of Water and Sanitation Programmes, Cox's Bazaar, Bangladesh, 21–25th November 1983.

[j] CAIRNCROSS, S. & CLIFF, J. *Water and health in Mueda, Mozambique*. Paper presented at the International Workshop on Measuring the Health Impacts of Water and Sanitation Programmes, Cox's Bazaar, Bangladesh, 21–25 November 1983.

[k] PICKERING, H. *The role of anthropologists in studying diarrhoea epidemiology: a case study from the Gambia*. Paper presented at the International Workshop on Measuring the Health Impacts of Water and Sanitation Programmes, Cox's Bazaar, Bangladesh, 21–25 November 1983.

[l] RAHAMAN, M. M. *The Teknaf Health Impact Study: methods and results*. Paper presented at the International Workshop on Measuring the Health Impacts of Water Supply and Sanitation Programmes, Cox's Bazaar, Bangladesh, 21–25 November 1983.

[m] See, for example, *World Health Statistics Report*, Vol. 26, No. 11, 1973; *World Health Statistics Report*, Vol. 29, No. 10, 1976; and *The International Drinking Water Supply and Sanitation Decade. Review of national baseline data (as at 31 December 1980)*, Geneva, World Health Organisation, 1984 (WHO Offset Publication No. 85).

programmes in urban areas, in some cases dating back thousands of years. Rural excreta disposal programmes are typically a new phenomenon, and some countries still lack concerted efforts in this sector. Problems commonly encountered in excreta disposal programmes include the inappropriate choice of technology, poor operation and maintenance, inadequate revenue collection, and the lack of perception in many rural communities of the importance of improved excreta disposal practices. Research into the technical, economic, and social aspects of excreta disposal in developing countries (e.g., see *47*) over the past decade has led to some promising new approaches.

COSTS

Despite the extensive experience with water supply and excreta disposal projects throughout the world, the cost data on these projects are often of poor quality and not strictly comparable. Data on operation and maintenance costs, on institutional overhead costs, and on the costs of community mobilization and education, are especially deficient.

Table 6 presents cost data from 87 developing countries. Costs vary widely depending upon the design criteria adopted in different countries and upon the costs of labour and materials. The costs of operation and maintenance (recurrent costs) must be added to the construction costs, and data on these costs are not readily available. One study of excreta disposal in 12 countries estimated that operation and maintenance accounted for between 4% and 52% of the total project costs per year, depending on the technology under consideration (*47*). Several widely used technologies (for instance, sewerage and pour-flush latrines) had operation and maintenance costs that comprised approximately 30% of the total annual project costs. For rural water supplies, data assembled by a UNDP/World Bank project[n] suggest that the same figure, 30%, is a reasonable estimate of the proportion of the total annual costs taken up by operation and maintenance. The 30% figure is adopted in Table 6 for both water supplies and excreta disposal.[o] Reliable data on the costs of software support (such as the promotion of community par-

[n] UNDP project INT/81/026.

[o] The computation of the percentage of total annual costs due to operation and maintenance requires the adoption of a discount rate (or opportunity cost of capital). Choosing the discount rate is partly a matter of judgement, and different economists may advocate different rates for the analysis of the same project. The choice of a high discount rate (say, 20%) will reduce the apparent importance of recurrent costs within total project costs. If a low discount rate (say, 5%) is chosen, perhaps to reflect the scarcity of recurrent funds (*5*), the proportion of total costs that is attributed to operation and maintenance will be greatly increased.

Table 6. Costs for urban and rural water supply and excreta disposal projects

Type of service	Construction cost per capita (1982, US$)[a]	Lifetime (years)[b]	Annual construction cost per capita (1982, US$)[c]	Annual total cost per capita (1982, US$)[d]
Water supply				
Urban				
House connection	116	20	14	20
Public tap	66	20	8	11
Rural[e]	60	20	7	10
Sanitation				
Urban				
Sewerage	174	50	18	26
Other	66	20	8	11
Rural	19	10	3	4

[a] Median values of the costs from 87 developing countries reported to WHO. For further information, see *The International Drinking Water Supply and Sanitation Decade. Review of national baseline data (as at 31 December 1980)*, Geneva, World Health Organization, 1984 (WHO Offset Publication No. 85).

[b] Commonly assumed values.

[c] Assuming an opportunity cost of capital (discount rate) of 10%.

[d] Assuming that construction costs are 70% of the total annual costs (see text).

[e] A variety of technologies are included here, but predominantly public taps and handpumps.

ticipation or hygiene education) and of apportioned institutional overheads have not been located, and so these costs, which are not trivial, have been omitted from the calculations.

Total annual costs per capita are derived in Table 6, assuming that recurrent costs comprise 30% of the total annual costs, that project lifetimes are between 10 and 50 years (depending upon the technology), and that the appropriate discount rate is 10%. The total annual costs per capita in Table 6 may be aggregated to derive the costs of complete water supply and excreta disposal interventions. For instance, a rural water supply and excreta disposal project might cost US$ 14 per capita annually ($10 + $4), whereas a combination of in-house water and sewerage in an urban area might have an annual cost of US$ 46 per capita ($20 + $26).

A goal of this series of reviews (*38*) is to derive cost-effectiveness estimates for each intervention. Special difficulties are inherent in applying the cost-effectiveness analysis to interventions having multiple benefits, and water supply and excreta disposal interventions present these difficulties in an extreme form (*9, 14*). In addition to their impact on diarrhoea rates among young children, these interventions may avert diarrhoea in other age groups, reduce the incidence of other infectious diseases, and have a variety of benefits unrelated to health. In view of this, a treatment of the cost-effectiveness of water supply and excreta disposal in relation to other diarrhoea control measures will be left to a later publication.

CONCLUSIONS

The results in Tables 2–4 show that substantial reductions in diarrhoea morbidity and mortality rates can be expected from investments in water supply and excreta disposal. Table 2 suggests that investments that improve both water quality and availability are especially effective. There are no adequate data on the impact of improvements in water quality plus availability together with excreta disposal. Likewise, the available data do not permit an assessment of the advantages of adding a hygiene education component to a project, but analysis of hygiene education alone suggests that it may further enhance the impact (*34*). Taking all this evidence together, and in view of the impact of large service-level improvements shown in Table 3, it is possible that well-designed projects combining water supply, excreta disposal and hygiene education may achieve diarrhoea morbidity rate reductions of 35–50%. It is to be expected that, in any given project, the impact on diarrhoea mortality rates will be larger than that on diarrhoea morbidity rates, except in areas where other interventions, such as oral rehydration programmes, have substantially reduced the risk of death from diarrhoea.

This review highlights some of the deficiencies in our knowledge of the impacts of water supply and excreta disposal on diarrhoea. More studies of these impacts are required, and it is expected that current advances in methodology[p] will enable such studies to be undertaken retrospectively and at reasonable cost. The model discussed under hypothesis 2 suggests that there may be advantages in measuring the impact on severe diarrhoea rather than all diarrhoea. Where etiology-specific studies are being conducted, they are more likely to record impacts on diarrhoea due to agents having high infectious doses than on diarrhoea due to agents having low infectious doses. The most pressing research need is to document the impact on diarrhoea of projects that combine improvements in water quality, water availability and excreta disposal with hygiene education that are functioning satisfactorily and are being utilized by the intended beneficiaries.[q]

[p] BRISCOE, J. ET AL. Measuring the impacts of water supply and sanitation projects on diarrhoea: prospects for case-control methods (in preparation).

[q] *Minimum evaluation procedure (MEP) for water supply and sanitation projects.* Unpublished document WHO/ETS/83.1, 1983.

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RÉSUMÉ

LA LUTTE CONTRE LES MALADIES DIARRHEIQUES DU JEUNE ENFANT: INTERVENTIONS VISANT À AMÉLIORER L'APPROVISIONNEMENT EN EAU ET L'ÉLIMINATION DES EXCRETA

Cet article est le neuvième d'une série d'analyses consacrées aux mesures possibles pour lutter contre les diarrhées. Dans les pays en développement, l'impact des projets d'approvisionnement en eau et d'évacuation des excreta sur les maladies diarrhéiques a été au centre de très nombreuses discussions et recherches. Quelques observations donnent à penser que des améliorations portant sur la qualité de l'eau, l'approvisionnement en eau, l'hygiène individuelle et l'évacuation des excreta, réduiraient l'ingestion des agents pathogènes à l'origine de diarrhées. On expose ici un modèle théorique qui établit une relation entre la quantité ingérée d'agents pathogènes responsables de diarrhées et la fréquence de ces affections dans la communauté.

Ce modèle montre que, dans des communautés pauvres, mal approvisionnées en eau et où l'évacuation des excreta se fait de façon insalubre, la diminution de la quantité d'agents entéropathogènes ingérée exerce, à valeur égale, un impact plus grand sur les taux de mortalité que sur ceux de morbité. Elle améliore davantage les diarrhées graves que les diarrhées bénignes et plutôt celles dont les agents étiologiques agissent à dose élevée.

Le recensement de 67 études effectuées dans 28 pays permet d'analyser l'impact de l'approvisionnement en eau et de l'évacuation des excreta sur les maladies diarrhéiques, les infections apparentées, l'état nutritionnel et la mortalité. Toutes ces études montrent une diminution médiane de 22% des taux de morbidité associés aux maladies diarrhéiques, la diminution atteignant 27% dans quelques études mieux conçues: pour le taux de mortalité global, la diminution médiane a été de 21%, atteignant 30% dans les quelques études mieux conçues. L'amélioration de la qualité de l'eau importante moins que celle de l'approvisionnement ou de l'évacuation des excreta. Mieux vaut améliorer la qualité de l'eau et l'approvisionnement qu'un seul de ces éléments ou que l'élimination des excreta. Les projets d'approvisionnement en eau et d'évacuation des excreta ont un impact plus important sur la shigellose que sur les infestations à *Entamoeba histolytica* ou à *Giardia lamblia*, mais on ignore quelles peuvent en être les répercussions sur les diarrhées causées par *Escherichia coli* entérotoxigène ou les rotavirus. Les six études portant sur les répercussions de l'approvisionnement en eau ou de l'évacuation des excreta sur l'état nutritionnel ont fait état d'une amélioration.

L'article présente ensuite une analyse des données sur les coûts de construction pour les projets d'approvisionnement en eau et d'assainissement dans 87 pays en développement. Si l'on ajoute les coûts d'exploitation et d'entretien, sans tenir compte des coûts liés à la mobilisation et à l'éducation de la communauté ni des frais généraux institutionnels, on arrive à un total médian de 14-46 dollars E.-U. (prix de 1982) par tête, selon l'importance du service.

Il faudra effectuer davantage d'études concernant l'impact des projects d'approvisionnement en eau et d'évacuation des excreta sur les maladies diarrhéques. En tout premier lieu, on étudiera l'impact de projets combinant une amélioration de la qualité de l'eau, de l'approvisionnement en eau et de l'évacuation des excreta à une education en matière d'hygiène, en s'intéressant à des installations qui donnent satisfaction et sont effectivement utilisées par les personnes visées.

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Interventions for the control of diarrhoeal diseases among young children: rotavirus and cholera immunization*

I. DE ZOYSA[1] & R. G. FEACHEM[2]

The potential effects of rotavirus and cholera immunization (with an improved vaccine) on diarrhoea morbidity and mortality among young children are reviewed using data from field studies and theoretical calculations. In developing countries rotavirus may be responsible for about 6% of all diarrhoea episodes and 20% of all diarrhoea deaths in children under 5 years of age. In industrial countries these proportions may be higher. Rotavirus immunization may reduce overall diarrhoea morbidity rates by 2–3% and diarrhoea mortality rates by 6–10% among children under 5 years of age in developing countries, depending on vaccine efficacy and programme coverage. The impact of improved cholera vaccines depends on the prominence of cholera as a cause of diarrhoea, and this varies greatly from country to country. Taking the extreme example of Bangladesh, where cholera is endemic and may account for about 0.4% of all diarrhoea episodes and 8% of all diarrhoea deaths in children under 5 years of age, cholera immunization might reduce overall diarrhoea morbidity rates by 0.06–0.13% and diarrhoea mortality rates by 1–2% among these children. The similar incidence rates in industrial and developing countries suggest that rotavirus diarrhoea may not be controlled by improvements in water supply, sanitation, or hygiene. Control may depend upon the widespread use of an effective vaccine.

Over recent years substantial resources have been invested into research to develop a vaccine against rotavirus diarrhoea and an improved vaccine against cholera. Rapid progress has been made and field trials of candidate vaccines against these diseases are under way. It is timely, therefore, to examine the potential role of rotavirus and cholera immunization in national programmes to reduce diarrhoea morbidity and mortality among children under 5 years of age. In this review we do not examine the potential benefits of rotavirus and cholera immunization that might extend to older children, adults, or especially susceptible or at-risk groups, nor do we consider the potential role of cholera immunization in epidemic control. Several recent reviews on the epidemiology and control of rotavirus diarrhoea (*41*, *83*) and cholera (*13*, *16*, *17*, *33*, *46*) provide a useful background to this more focused analysis. This paper is the seventh in a series of reviews of potential anti-diarrhoea interventions published in the *Bulletin of the World Health Organization* (*1*, *15*, *18–22*).

EFFECTIVENESS

For rotavirus or cholera immunization to be an effective intervention for the control of diarrhoeal diseases it must be true that:

either

a considerable proportion of diarrhoea morbidity or mortality in young children is caused by rotavirus or *Vibrio cholerae* O1	*hypothesis 1*

and

vaccines against rotavirus, *V. cholerae* O1, or their products have the potential to reduce morbidity rates or mortality rates or the severity of diarrhoea caused by these organisms	*hypothesis 2*

* Requests for reprints should be addressed to the Director, Diarrhoeal Diseases Control Programme, World Health Organization, 1211 Geneva 27, Switzerland.

[1] Save the Children Fund Research Fellow, Department of Tropical Hygiene, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, England.

[2] Head, Department of Tropical Hygiene, London School of Hygiene and Tropical Medicine, London, England.

or

rotavirus or cholera immunization (when effective vaccines are available) has the potential to reduce overall diarrhoea morbidity rates or mortality rates or the severity of diarrhoea in young children	*hypothesis 3*

The potential effectiveness of rotavirus or cholera immunization in the control of diarrhoeal diseases would be suggested by a demonstration either of the correctness of hypotheses 1 and 2, or of the correctness of hypothesis 3. The evidence for and against the three hypotheses is examined below.

Hypothesis 1. *A considerable proportion of diarrhoea morbidity or mortality in young children is caused by rotavirus or* V. cholerae *O1.*

Rotavirus

Rotavirus-associated morbidity. We have located in the literature only 7 prospective, community-based studies that have assessed the importance of rotavirus diarrhoea among children in the community (Table 1). Four studies (*6, 7, 31, 49*) report the incidence rates of rotavirus-associated diarrhoea and rotavirus isolation rates, and three others (*30, 53, 68*) give only the isolation rates. Multiple infections were common in all the studies: other enteric pathogens were detected in up to half of all episodes of rotavirus-associated diarrhoea. The data in Table 1, as far as possible, refer only to episodes where rotavirus was the sole recognized enteric pathogen. In some studies, stools were not examined for some common pathogens such as enterotoxigenic *Escherichia coli* (ETEC) (*49*) and *Campylobacter jejuni* (*6, 7, 31, 49, 68*).

Recorded incidence rates of rotavirus-associated diarrhoea ranged from 0.2 to 0.8 episodes per child per year. Incidence rates were low in children aged 0–5 months, reached a peak in children aged 6–11 months, remained high in children aged 12–23 months, and dropped to low levels thereafter. It is notable that the incidence rate of rotavirus-associated diarrhoea found in the study from Winnipeg, Canada (0.3 episodes per child per year among children aged 0–23 months) (*31*) was similar to the rate reported from Bangladesh in the same age group (0.4 episodes per child per year) (*6*). The incidence of all diarrhoeas, however, was lower in Canada and the proportion of diarrhoea episodes associated with rotavirus was accordingly higher.

We estimate that, in developing countries, rotavirus accounts for about 8% of all diarrhoea episodes in children aged 0–5 months, 10% in children aged 6–23 months, 1% in children aged 24–59 months, and 6% in children under 5 years. These figures are used in the computations below. In a particular country, where more reliable age-specific proportions are available, other figures may be substituted. It will be noted that the incidence rate of rotavirus-associated diarrhoea found in different studies (Table 1) did not vary as much as the incidence

Table 1. Community-based studies of rotavirus-associated diarrhoea

Country	Age (months)	Number of person-years	Number of episodes of:		Proportion of diarrhoea episodes associated only with rotavirus (%)	Reference
			Diarrhoea from all causes	Diarrhoea associated with rotavirus alone		
Bangladesh	0–23	112	377 (3.4)[a]	43 (0.4)	11	*6*
	24–59	112	243 (2.2)	0	0	
Bangladesh	2–23	77	497 (6.4)	32 (0.4)	6	*7*
	24–59	92	444 (4.8)	3 (0.03)	0.7	
Brazil	All ages	765	1097 (1.4)	– (0.15)[b]	11	*30*
Canada	0–23	139	165 (1.2)	40 (0.3)	24	*31*
El Salvador	0–35	–	–	–	7	*68*
Guatemala	0–35	132	1050 (7.9)	109 (0.8)	10	*49*
USA	0–23	–	–	–	10	*53*

[a] Figures in parentheses are the number of episodes per person-year.
[b] Estimated incidence rate.

rate of diarrhoea from all causes. The proportion of all diarrhoea episodes attributable to rotavirus is likely to be greater than our estimate in settings where the incidence rate of diarrhoea from all causes is low, and smaller where the incidence rate of diarrhoea from all causes is high.

To assess the impact of rotavirus diarrhoea on the health services, rotavirus isolation rates reported in 77 hospital-based studies from 37 countries have been reviewed.[a] Caution is necessary in the interpretation and comparison of these rates. Different diagnostic methods were used for the detection of rotavirus and the findings were reported in different age groups. Many studies did not span an entire year, and large seasonal fluctuations in rotavirus isolation rates are well documented. Bearing these factors in mind, we see that in nearly all the studies rotavirus was the single most common enteric pathogen identified in children attending hospital for the treatment of diarrhoea.

In studies of hospitalized children that lasted at least one year, the median isolation rate was 34% (range, 12–71%). The median rate was similar in studies from developing and industrial countries (respectively, 35% and 34%; with ranges, 16–71% and 12–65%). In general, the age-specific isolation rates were low in infants aged 0–5 months, reached a peak in infants aged 6–11 months, remained high in children aged 12–23 months, and dropped rapidly thereafter. Because a considerable proportion of all diarrhoea cases that are admitted to hospital occur in infants, most rotavirus-positive cases were found in this age group. Indeed, in a number of studies, large numbers of rotavirus-positive cases were found among hospitalized children aged 0–5 months, despite low isolation rates in this age group. Among the 19 studies that reported these data the proportion of all rotavirus-positive cases among hospitalized children aged 0–23 months that occurred in the first 6 months of life ranged from 4% (*62*) to 73% (*57*), with a median of 35%. We have located only 5 studies in which the data are examined in narrower age-bands. In these studies, the proportion of all rotavirus-positive cases among infants (0–11 months) admitted to hospital for diarrhoea that occurred in the first 3 months of life ranged from 11% to 37%, with a median of 26% (*2*, *36*, *57*, *58*, *74*).

Studies conducted among children treated for diarrhoea on an outpatient basis or in short-stay rehydration units reported lower rotavirus isolation rates. In studies that lasted at least one year the median rate found among these patients was 28% (range, 10–49%). Where outpatients and inpatients were examined concurrently the rates were found to be lower among outpatients. This finding is difficult to interpret because the two groups of patients were not strictly comparable in all studies (*8*).

Two studies have assessed population-based hospital case rates. In Washington, DC, USA (*66*), a population of about 29 000 children aged 0–14 years was defined whose primary health care was provided by a health maintenance organization. Over a period of 27 months, 38 children from the health maintenance organization were admitted to hospital for the treatment of diarrhoea. Rotavirus was recovered from 60% of cases. Yearly population-based hospitalization rates for rotavirus-associated diarrhoea were 3.7 per thousand in infants and 2.2 per thousand in children aged 12–23 months, and dropped to 0.2 per thousand in children aged 24–59 months. Hospitalization for rotavirus-associated diarrhoea was not observed after 5 years of age. In a district of Copenhagen County, Denmark (*32*), rotavirus was detected among 37% of children aged 0–14 years admitted to the district hospital because of diarrhoea over a 12-month period. Yearly population-based hospitalization rates for rotavirus-associated diarrhoea were 5.4 per thousand in infants, 4.1 per thousand in children aged 12–23 months, and 1.4 per thousand in children aged 24–47 months. No admissions for rotavirus-associated diarrhoea were observed in children over 4 years of age.

Thus, despite low isolation rates in the community, rotavirus is responsible for about one-third of diarrhoea episodes that require hospital admission among young children, suggesting that diarrhoea caused by rotavirus is of above-average severity. Prospective studies of diarrhoea episodes acquired in the community provide evidence that rotavirus-associated diarrhoea leads more frequently to dehydration and attendance at a health facility than all other diarrhoeas in the same age group (*6*, *7*, *49*, *81*). In these studies, although the incidence of rotavirus-associated diarrhoea was low, rotavirus was responsible for about half of all dehydrating episodes.

Rotavirus-associated mortality. Rotavirus-associated diarrhoea may therefore take on severe forms and is clearly responsible for a proportion of all deaths due to diarrhoea. Diarrhoea mortality rates are low in industrial countries, yet fatal episodes of diarrhoea associated with rotavirus have been described. Over a 5-year period, 21 deaths associated with rotavirus were recorded among young children in Toronto, Canada (*10*). The severe course of the diarrhoea was highlighted by the fact that all deaths occurred within 3 days of onset of symptoms and that the parents of 16 of the children had had some contact with a physician during the course of their child's illness. Similarly, in the course of an explosive

[a] Tabulated data and sources are available on request from R.G.F.

Table 2. The proportion of diarrhoea deaths in the first five years of life associated with rotavirus in developing countries, based on various assumptions

Age (months)	Distribution of 100 diarrhoea deaths[a]	Proportion that are acute watery diarrhoea deaths[b] (%)	Number of acute watery diarrhoea deaths	Proportion of acute watery diarrhoea deaths that are associated with rotavirus[c] (%)	Number of rotavirus-associated diarrhoea deaths
0–5	29	60	17	20	3.4
6–11	16	60	10	50	5.0
12–23	35	60	21	50	10.5
24–59	20	50	10	10	1.0
0–59	100		58		19.9

[a] These calculations assume that diarrhoea mortality rates are 20 per 1000 per year in the 0–11-month age group, 18 per 1000 per year in the 12–23-month age group, and 4 per 1000 per year in the 24–59-month age group (derived from ref. *67*). Overall mortality rates vary greatly from country to country. Values adopted here are: infant mortality rate 120 per 1000 live births, mortality rate 40 per 1000 per year in the 12–23-month age group, and 10 per 1000 per year in the 24–59-month age group. It is further assumed that 66% of infant diarrhoea deaths occur in the first 6 months of life (the median figure from 8 studies).

[b] Estimates based on data from Oberle et al. (*60*) and Chen et al. (*12*).

[c] Estimates based on data in the text on the proportion of hospitalized diarrhoea cases and the proportion of dehydrated diarrhoea cases seen in the community, which were associated with rotavirus.

outbreak of 3439 reported cases of rotavirus-associated diarrhoea in an isolated Pacific island group (*24*), 7 children died, all from dehydration due to diarrhoea and vomiting and all within the first 4 days of illness.

For developing countries, where mortality due to diarrhoea is considerable (*67*), we have theoretically derived the proportion of all diarrhoeal deaths that are associated with rotavirus. On the basis of the calculations set out in Table 2, rotavirus may, in developing countries, account for about 12% of all diarrhoea mortality in infants aged 0–5 months, 30% in children aged 6–23 months, 5% in children aged 24–59 months, and 20% in children under 5 years.

Cholera

The prominence of cholera varies greatly from country to country. In this review we consider the extreme case of Bangladesh, where cholera is endemic and has been studied intensively over a number of years.

Cholera morbidity in Bangladesh. Table 3 summarizes data from six studies from Dhaka and Matlab

Table 3. Community-based studies of cholera in Bangladesh

Place	Dates of study	Age groups	Cholera incidence rate (episodes per 1000 per year)	Proportion of diarrhoea episodes associated with *V. cholerae* 01 (%)	Reference
Dhaka	Sep. 75 to Dec. 76	All ages	3	0.7	*54*
Matlab	Nov. 63 to June 66	0–59 months All ages	10 3	– 0.7	*50*
Matlab	July 69 to June 70	0–11 months 12–59 months All ages	0 9 3	– – –	*56*
Matlab	Dec. 77 to Nov. 78	0–23 months 2–9 years	– –	< 2[a] < 3[a]	*6*
Matlab	March 78 to March 79	2–59 months	–	0.3	*7*

[a] This proportion refers to all infections with enteric pathogens other than ETEC, *Shigella* and rotavirus, and to mixed infections.

Table 4. *Vibrio cholerae* isolation rates among diarrhoea cases in hospitals in Bangladesh

Place	Dates of study	Type of patient	Age groups	*V. cholerae* 01 isolation rates (%)	Reference
Dhaka	July 64 to June 66	Inpatients	All ages	40	*48*
Dhaka	Dec. 79 to Nov. 80	Outpatients and inpatients	0–11 months 12–59 months All ages	1 6 6	*69*
Matlab	Nov. 63 to June 66	Inpatients	All ages	25	*50*
Matlab	July 69 to June 70	Outpatients and inpatients	All ages	27	*56*
Matlab	Jan. 75 to Dec. 75	Inpatients	0–11 months 12–59 months All ages	1 27 28	*60*
Matlab	Feb. 77 to Jan. 79	Outpatients and inpatients	0–23 months 2–9 years All ages	2 31 13	*5*

in which surveillance of cholera was conducted in the community. Three studies recorded cholera incidence rates, which were very low at 3 episodes per thousand per year. Rates were highest in children aged 12–59 months and lowest in infants. Overall, the proportion of all diarrhoea episodes associated with *V. cholerae* O1 was less than 1%. For the computations that follow it will be assumed that, in Bangladesh, cholera accounts for 0.2% of diarrhoea episodes in children under 2 years of age, 0.6% in children aged 24–59 months, and 0.4% in children under 5 years of age.

Table 4 lists the *V. cholerae* O1 isolation rates reported in hospital-based studies conducted in Dhaka and Matlab. The proportion of diarrhoea episodes associated with *V. cholerae* ranged from 6% to 40% according to the hospital and the year of study. We cannot tell from these data whether the *V. cholerae* isolation rates were lower in outpatients than inpatients, but there is evidence to suggest that patients presenting to hospital with cholera have a greater risk of moderate or severe dehydration requiring inpatient therapy than other patients (*5*, *69*). *V. cholerae* isolation rates were low in the first 2 years of life and reached a peak in children over 5 years of age.

Three studies have assessed population-based hospital case rates. Martin et al. (*48*) analysed the admissions to the Dhaka diarrhoeal diseases hospital between July 1964 and June 1966 and found a hospitalization rate for classical cholera of 0.4 admissions per thousand population per year with a peak rate of 0.7 per thousand per year in children below 5 years of age. The hospitalization rate for cholera (mainly eltor) in the same hospital was 1.7 admissions per thousand population in 1974 and 1.4 in 1975 (*44*), with the highest rates in children aged 2–9 years. Glass et al. (*25*) examined the attendance at Matlab hospital for the 15-year period between January 1966 and December 1980. In that period, *V. cholerae* O1 was isolated from 7141 of the more than 50 000 patients who presented to the hospital with diarrhoea. From 1966 to 1973, 97% of the *V. cholerae* isolates were of the classical biotype. The eltor biotype was first identified in the Matlab area in 1969 and was the only biotype present from 1973 to the end of the study. There was great year-to-year variation in the number of cases, particularly during the eltor period. The overall attendance rate for cholera in the classical period was 1.3 patients per thousand per year and in the eltor period 2.9 patients per thousand per year, with the highest rates in children aged 2–9 years.

Cholera, then, presents an extreme case of a diarrhoeal disease that is rare in the community but may nevertheless place a considerable burden on the health services. In a study conducted in Matlab (*50*), cholera accounted for only 0.7% of all diarrhoea episodes acquired in the community, yet 25% of all hospital admissions for treatment of diarrhoea during the same period were associated with *V. cholerae*. Other data from Bangladesh indicate that the proportion of cholera cases that require hospitalization varies between 23% and 74% and is higher for classical than for eltor cholera (*3*, *42–44*, *61*, *78*, *79*). These findings support the view that cholera is an unusually severe disease.

Cholera mortality in Bangladesh. There are no data on cholera mortality rates in Bangladesh. In the study areas, deaths due to acute diarrhoea are very rare in hospital and those that occur in the community have no etiological diagnosis. For the computations that follow it will be assumed that, in Bangladesh, cholera accounts for 5% of diarrhoea deaths in children under 2 years of age, 20% in children aged 24–59 months, and 8% in children under 5 years of age. These estimates are based on data summarized in Table 4 on the proportion of hospitalized diarrhoea cases that is associated with *V. cholerae* in different age groups in Bangladesh.

Hypothesis 2. *Vaccines against rotavirus,* V. cholerae *O1, or their products have the potential to reduce morbidity rates or mortality rates or the severity of diarrhoea caused by these organisms.*

Rotavirus vaccines. Mechanisms of immunity to rotavirus and advances in rotavirus vaccine development have recently been reviewed (*41*). To date, research has focused on the development of live attenuated human rotavirus vaccines, live rotavirus vaccines from animal hosts, and live attenuated reassortant vaccines, for delivery by the oral route. Each of the four recognized human rotavirus serotypes has now been successfully cultivated (*85*), and live attenuated human rotavirus vaccines can be prepared by conventional tissue-culture methods. A tissue-culture-adapted mutant of the Wa strain of human rotavirus (*82*) is under evaluation for immunogenicity and safety in susceptible volunteers (*39, 40*). Cold-adapted strains of human rotavirus are also under investigation as attenuated human rotavirus vaccines (Kono, personal communication, 1984). In addition, strains obtained from asymptomatically-infected neonates are under study as naturally attenuated strains (Bishop, personal communication, 1984). These strains are promising candidate vaccines in view of the evidence that immunity induced by neonatal infection prevents the development of clinically severe illness for at least the first 3 years of life (although it does not protect against infection) (*4*).

Another approach is to prepare vaccine material from animal rotavirus strains that are antigenically related to human rotavirus (*35, 38, 84*). Bovine rotaviruses grow well in tissue culture (*51*) and have been used to prepare candidate vaccines. The feasibility of this approach was demonstrated in experimental studies in animals (*80, 86, 88*). A rotavirus vaccine of bovine origin (strain RIT 4237) was shown to be immunogenic and safe in young children (*75*) and a field trial in a group of Finnish children aged 8–11 months using one dose of vaccine of high titre ($10^{8.1}$TCID$_{50}$) showed a protective efficacy of 50% for all rotavirus-associated diarrhoea and of 88% for rotavirus-associated diarrhoea lasting more than 24 hours (*76*). In a subsequent trial in which 2 doses of vaccine were given one month apart to Finnish children aged 6–12 months, vaccine efficacy was found to be 58% for all rotavirus-associated diarrhoea and 82% for rotavirus-associated diarrhoea that was clinically significant (Vesikari, personal communication, 1984). Infants who seroconverted appeared to have the highest level of protection, but protection was also observed in infants who did not seroconvert. Seroconversion rates may be improved by giving a milk feed (infant formula or diluted cow's milk) immediately before and after vaccination (*77*). Further field trials with this vaccine are under way in Peru and the Gambia. Another promising candidate vaccine is a rhesus rotavirus strain (*70, 84*) which has been tested for immunogenicity and safety in human volunteers and is now under field trial in the USA. Finally, reassortant viruses have been recovered from mixed tissue-culture infection (*27–29*), opening the way to the development of a live attenuated reassortant rotavirus vaccine.

In conclusion, good progress has been made in the development of candidate rotavirus vaccines using different approaches. Further candidate vaccines may be developed using recombinant DNA technology. Field trials of rotavirus vaccines of bovine and simian origin are under way. These vaccines appear to prevent or modify rotavirus-associated illness. Studies in progress will assess the duration of protection induced by these vaccines and their strain specificity. The optimal age of vaccination must be determined, bearing in mind the need to vaccinate infants in the first 6 months of life, and the possible interference of breast-feeding or of residual maternal antibodies on seroconversion rates. Information is also needed on the number of doses required in order to determine the most appropriate vaccination schedule, with regard to production and delivery costs and eventual combination with oral polio vaccine. Other issues to be addressed concern the stability of the rotavirus vaccine, its cold-chain requirements, and its possible interaction with oral polio vaccine.

Cholera vaccines. Advances in cholera vaccine development have recently been reviewed (*46*). The ideal antigenic composition of an effective oral cholera vaccine is not at present known (*13*) and work is under way to identify the major protective somatic and toxin-derived antigens. The only vaccines currently available for general use are killed whole-cell vaccines for parenteral administration. Field trials with these vaccines have established that induced protection is moderate (50–70%) and of short duration (3–6 months), depending on the age group, quality of the vaccines, and dosage schedule

(*23*). Current research efforts are centred on the development of a cholera vaccine for oral use, in order to stimulate local intestinal immunity and to avoid a possible suppressive effect of parenteral immunization on local antigenic stimulation (*64*, *87*). Whole-cell vaccines taken orally afford some (56%) degree of protection against experimental cholera and reduce the severity of diarrhoea in ill volunteers (*11*; Levine, personal communication, 1984). A whole-cell vaccine for oral use is currently under field trial in Bangladesh. Another killed oral vaccine has been prepared by ultrafiltration of the culture supernatant of two eltor strains of *V. cholerae* O1. Results from a field trial in Zaire suggest that this vaccine may have protective properties against natural disease.[b]

The immunogenicity and efficacy of toxin derivatives have also been evaluated. Field trials of parenterally administered toxoids, consisting of purified cholera toxin inactivated with either formaldehyde or glutaraldehyde, have demonstrated slight or no protection against cholera (*14*, *59*). In volunteers, large, multiple oral doses of purified toxoid are safe and immunogenic but have failed to provide protection against experimental challenge (*45*). Procholeragenoid, a heat-induced aggregate of cholera toxin (*46*) and the purified B subunit of cholera toxin (*26*, *72*) are safe and immunogenic in volunteers but their protective effects have not yet been reported.

Animal studies have shown that antibacterial and antitoxic intestinal antibodies are synergistically protective (*63*, *65*, *71*), suggesting that a vaccine prepared from a combination of somatic and toxin-derived antigens holds promise. One approach is to develop attenuated *V. cholerae* strains for use as oral vaccines. Studies have been carried out on Texas Star-SR, an attenuated strain derived by chemical mutagenesis from an eltor Ogawa organism (*34*). Texas Star-SR produces the B subunit of cholera toxin but no detectable A subunit. In US volunteers it was shown to provide a moderate (61%) degree of protection against experimental challenge with *V. cholerae* and to reduce the stool volume in ill vaccinees (*47*). Unfortunately, 24% of vaccinees had mild or moderate diarrhoea. Of further concern is the fact that the precise genetic lesion responsible for the inability of the strain to elaborate cholera toxin is unknown, and reversion is theoretically possible.

Recombinant DNA techniques have been applied to develop attenuated *V. cholerae* oral vaccine strains incapable of genetic reversion (*37*, *52*). Precise deletions of the genes encoding both the A and B subunits of cholera toxin have produced a strain (JBK-70) that protects volunteers from subsequent challenge to a degree (89%) similar to recovery from the disease (*46*). This strain, however, was also associated with diarrhoea in an unacceptable proportion of recipients. Research is under way to identify the factors responsible for the observed side-effects.

Another approach is to prepare an oral killed vaccine containing a combination of somatic and toxin-derived antigens. Studies in volunteers of vaccines prepared from killed whole-cell vibrio combined with procholeragenoid or glutaraldehyde-treated toxoid have demonstrated complete safety and protective efficacy rates of 27% (with procholeragenoid) and 67% (with toxoid) (*46*). A combined B subunit and killed whole-cell oral vaccine has been shown to be safe in volunteers in Bangladesh and Sweden, and capable of inducing in Bangladeshi volunteers a local immunological response comparable to that evoked by the disease (*73*). Subsequent challenge studies among US volunteers demonstrated a vaccine efficacy of 64% and complete protection against severe disease (*46*). Field trials of the combined B subunit/whole-cell vaccine and whole-cell vaccine alone are in progress in Bangladesh to determine the protective efficacy of the vaccines and the duration of protection in an endemic area. A number of issues remain unresolved, as with rotavirus vaccine, concerning especially the influence of age, breast-feeding practices, and residual maternal antibodies on protection.

Hypothesis 3. *Rotavirus or cholera immunization (when effective vaccines are available) has the potential to reduce overall diarrhoea morbidity rates or mortality rates or the severity of diarrhoea in young children.*

At present, the only approach to assessing hypothesis 3 is a theoretical one using information computed during the assessment of hypotheses 1 and 2.

Rotavirus immunization. The potential impact of rotavirus immunization on overall diarrhoea rates in children under 5 years will depend upon the age of immunization, vaccine efficacy, and programme coverage. The recommended vaccination schedule will be determined when data are obtained on dose requirements, the effect of breast-feeding and residual maternal antibodies, and the effect of interaction with antigens delivered in the context of the Expanded Programme on Immunization (EPI). The goal of rotavirus immunization programmes will be to vaccinate children as early as possible, but operational and immunological factors may prevent the achievement of full immunization before 6 months of age. Field trials of the RIT 4237 rotavirus vaccine in Finland have shown efficacies of 50–58%

[b] BWANGA, M. [First controlled trials of oral anticholera vaccine during a cholera epidemic in the zone of Matemba – Nkulu (Shaba-Zaire).] *Bulletin de la Société de Pathologie éxotique*, 77: 13–16 (1984) (in French).

Table 5. Maximum impact of rotavirus immunization on diarrhoea morbidity and mortality rates among children under 5 years of age in developing countries, assuming 100% vaccine efficacy, 100% programme coverage, and an average age of full immunization of 6 months[a]

Age (months)	Proportion of diarrhoea episodes		Proportion of diarrhoea deaths	
	Caused by rotavirus[b] (%)	Averted by rotavirus immunization (%)	Caused by rotavirus[c] (%)	Averted by rotavirus immunization (%)
0–5	8	0[d]	12	0[d]
6–23	10	10	30	30
24–59	1	1	5	5
0–59	6	5[e]	20	16[f]

[a] The computed proportions of episodes and deaths averted are directly proportional to the vaccine efficacy and the programme coverage, and thus the effects of different values for these parameters may be readily computed.

[b] See text.

[c] See Table 2.

[d] Average age of full immunization assumed to be 6 months.

[e] These calculations assume that diarrhoea morbidity rates are 3 per child per year in the 0–5-month age group, 4 per child per year in the 6–11-month age group, 4 per child per year in the 12–17-month age group, 3 per child per year in the 18–23-month age group, and 2 per child per year in the 24–59-month age group (derived from ref. *67*).

[f] Based on age-specific diarrhoea mortality rates given in footnote *a* to Table 2.

against all rotavirus-associated diarrhoea and 82–88% against rotavirus-associated diarrhoea of clinical significance in children aged 6–12 months (*76*; Vesikari, personal communication, 1984). In an ongoing immunization programme aimed at younger children the efficacy rates may be lower. An efficacy of rotavirus vaccine of 80% is assumed here. The proportion of children who would receive the vaccine depends on programme coverage. Three coverage figures are adopted here (45%, 60% and 75%), bearing in mind that these figures are not now being achieved in countries with limited immunization programmes, but may be expected in countries committed to the EPI and with a national programme built up over several years.

The proportions of all diarrhoea cases and deaths averted by rotavirus immunization are directly proportional to both vaccine efficacy and programme coverage, but not to age of immunization. Table 5 presents computations of the maximum impact of rotavirus immunization at 6 months of age on overall diarrhoea morbidity and mortality rates in developing countries, assuming 100% efficacy and 100% programme coverage. Under these ideal conditions, rotavirus immunization might reduce diarrhoea morbidity rates by 5% and diarrhoea mortality rates by 16% among children under 5 years of age. With a vaccine having 80% efficacy and levels of coverage of 45%, 60% and 75%, rotavirus immunization might reduce diarrhoea morbidity rates, respectively, by 1.8%, 2.4% and 3.0% and diarrhoea mortality rates by 6%, 8% and 10%. If immunization against rotavirus is completed at a younger age, say 3 months, the potential reductions in diarrhoea morbidity and mortality rates may only be marginally greater: 1.9–3.3% for morbidity and 6–11% for mortality (assuming that half of the diarrhoea episodes and deaths that occur in the first 6 months of life occur in the first 3 months of life; calculations not shown). The proportional impact of rotavirus immunization on diarrhoea morbidity rates among young children in industrial countries is likely to be greater because the proportion of diarrhoea episodes attributable to rotavirus in those countries is higher. The difference may not be marked for reductions in mortality rates, however, judging from the similar isolation rates for rotavirus found among young children admitted to hospital for severe diarrhoea in developing and industrial countries.

Two major hospital-based studies have been examined to assess the potential reduction in hospital reporting rates for diarrhoea that might be achieved by a rotavirus immunization programme. Data from a one-year study of patients reporting to the diarrhoeal diseases hospital in Dhaka, Bangladesh (*69*) suggest that rotavirus immunization might have averted 7–12% of attendances for diarrhoea to the hospital among children under 5 years of age. Data from an 8-year study of inpatients in a children's hospital in Washington, DC, USA (*9*) suggest that

Table 6. Maximum impact of cholera immunization on diarrhoea morbidity and mortality rates among children under 5 years of age in Bangladesh, assuming 100% vaccine efficacy, 100% programme coverage, and an average age of full immunization of 2 years[a]

Age (months)	Proportion of diarrhoea episodes		Proportion of diarrhoea deaths	
	Caused by *V. cholerae* 01[b] (%)	Averted by cholera immunization (%)	Caused by *V. cholerae* 01[c] (%)	Averted by cholera immunization (%)
0–23	0.2	0[d]	5	0[d]
24–59	0.6	0.6	20	20
0–59	0.4	0.3[e]	8	4[f]

[a] The computed proportions of episodes and deaths averted are directly proportional to the vaccine efficacy and the programme coverage and thus the effects of different values for these parameters may be readily computed.

[b] See text.

[c] See text.

[d] Average age of full immunization assumed to be 2 years.

[e] Based on age-specific diarrhoea morbidity rates given in footnote *e* to Table 5.

[f] Based on age-specific diarrhoea mortality rates given in footnote *a* to Table 2.

rotavirus immunization might have averted 9–14% of admissions for diarrhoea over that period. These calculations assume a vaccine efficacy of 80%, coverage of 45–75%, and an average age of full immunization of 6 months.

Cholera immunization. In Bangladesh, cholera may account for about 0.4% of all diarrhoea morbidity and 8% of all diarrhoea mortality in children under 5 years of age. Again, values for the efficacy of a new cholera vaccine have to be assumed. A protective efficacy of 64% has been found in challenge studies among adult US volunteers receiving 3 oral doses of combined B subunit/whole-cell vaccine (*46*). A value for the efficacy of a new cholera vaccine of 70% is assumed here. The vaccination schedule for this vaccine is unknown at present. If a new vaccine does not give long-lasting protection, the optimal age of administration may be around 24 months, before the peak in age-specific cholera incidence rate. In this case it will not be delivered within the existing EPI and so coverage may be low. Three coverage figures are adopted here: 30%, 45% and 60%.

Table 6 presents computations of the maximum impact of cholera immunization at 2 years of age on overall diarrhoea morbidity and mortality rates in Bangladesh, assuming 100% vaccine efficacy and 100% programme coverage. Under these ideal conditions, cholera immunization might reduce overall diarrhoea morbidity rates by 0.3% and diarrhoea mortality rates by 4% among children under 5 years of age in Bangladesh. With a vaccine having 70% efficacy and levels of coverage of 30%, 45% and 60%, cholera immunization at 2 years of age might reduce diarrhoea morbidity rates by 0.06%, 0.09% and 0.13% and diarrhoea mortality rates by 0.8%, 1.3% and 1.7%. If immunization against cholera is achieved at a younger age, say 6 months, and accordingly better coverage figures are adopted (45%, 60% and 75%), the potential reductions would be 0.11–0.19% for diarrhoea morbidity rates and 2.1–3.4% for diarrhoea mortality rates (calculations not shown).

In this review, we do not examine the benefits of cholera immunization that might extend to older children and adults in endemic areas if immunity induced by an improved vaccine is long-lasting, nor do we consider the potential role of cholera immunization in epidemic control[c] and in the protection of especially susceptible or at-risk groups. Finally, there are insufficient data to assess the exciting possibility that a vaccine prepared from antigens derived from cholera toxin may induce cross-protection against ETEC (LT-only or LT-ST) diarrhoea.

Cholera immunization may not have a measurable impact on hospital attendance rates for diarrhoea among young children. Data from the hospital-based study in Dhaka cited above (*69*) suggest that cholera immunization might have averted only 0.6–1.2% of attendances for diarrhoea among children under 5 years of age. Among older patients these potential reductions in attendances are 2–4%, assuming repeated vaccinations or long-lasting immunity.

[c] The role of immunization in the prevention and control of cholera epidemics will be considered in another review (Blake and Feachem, under preparation).

These calculations assume a vaccine efficacy of 70%, coverage of 30–60%, and an average age of full immunization of 2 years.

FEASIBILITY

The delivery requirements of the candidate rotavirus and cholera vaccines are at present unknown. The simultaneous administration of rotavirus vaccine with another vaccine currently included in the EPI would facilitate its delivery. Three doses of oral polio vaccine are usually recommended in the first 6 months of life and it is hoped that rotavirus vaccine can be combined with one or all 3 doses of oral polio vaccine without interference with seroconversion to either virus. The cold-chain and handling requirements of rotavirus and oral polio vaccines are likely to be similar. In this optimal case, rotavirus immunization would require few additional inputs for its delivery.

The delivery requirements of cholera vaccine are more speculative. A killed cholera vaccine may prove to be relatively temperature-stable, whereas a live cholera vaccine may have stringent cold-chain requirements. Cholera immunization with an improved vaccine may be indicated in the second year of life and may involve multiple doses. Cholera vaccine would not, in this case, be delivered within the EPI, but would require additional immunization services. The main operational difficulty would be achieving high coverage of children in this older age group. If a new cholera vaccine can induce long-lasting protection, its delivery will be greatly simplified.

Finally, a major constraint on the successful delivery of oral vaccines against both rotavirus diarrhoea and cholera would be the need to protect the vaccine against gastric acidity, in order to assure its safe passage into the small intestine.

COSTS

Rotavirus and improved cholera vaccines are still under development, so the cost estimates must be derived from data on current immunization programmes. In a recent review, Creese (under preparation) has estimated the likely costs of delivering these new vaccines on the basis of data from 9 cost-appraisal studies of immunization programmes in developing countries. Costs depend heavily on the extent to which the new vaccines can be incorporated into an existing immunization programme. The actual vaccine costs for current EPI vaccines account for only a small proportion (around 10%) of total programme costs.

Assuming an optimal delivery strategy for rotavirus immunization, in which a single dose of rotavirus vaccine is administered within an existing EPI programme without increased frequency of contacts, the likely marginal cost is US$ 2 (1982 prices) per fully immunized child. If cholera immunization requires additional contacts because it is targetted at a different age group than the EPI, estimated costs are from US$ 5 (if a single dose is required) to US$ 15 (if three doses are required) per child fully immunized against cholera (1982 prices). It is here assumed that the cost per vaccinated child is independent of the number of children vaccinated, within likely limits.

These cost estimates can be brought together with the effectiveness data computed above in order to calculate the likely cost-effectiveness range of the proposed interventions in developing countries. Two indicators of cost-effectiveness are considered here: cost per case averted and cost per death averted.[d]

For rotavirus immunization at age 6 months with a vaccine having 80% efficacy and a marginal cost of US$ 2 per fully immunized child, the cost-effectiveness figures are:

— US$ 4 (1982 prices) per diarrhoea case averted in a child aged 0–59 months;
— US$ 312 (1982 prices) per diarrhoea death averted in a child aged 0–59 months.

For cholera immunization at age 2 years in Bangladesh with a vaccine having 70% efficacy and a cost of US$ 5–15 per fully immunized child, the cost-effectiveness figures are:

— US$ 183–549 (1982 prices) per diarrhoea case averted in a child aged 0–59 months;
— US$ 3571–10 714 (1982 prices) per diarrhoea death averted in a child aged 0–59 months.

If cholera immunization is achieved at 6 months of age at the marginal cost of US$ 2–6 per fully immunized child, the likely cost-effectiveness of the intervention is greatly improved (cost per case averted US$ 61–183 and cost per death averted US$ 872–2617).

CONCLUSIONS

In developing countries, rotavirus may be responsible for about 6% of all diarrhoea episodes and 20% of all diarrhoea deaths in children under 5 years of age. In industrial countries these proportions may be higher. A theoretical case has been made, based on various assumptions about vaccine efficacy and

[d] The formulae used to calculate these cost-effectiveness figures are available on request from R.G.F.

programme coverage, that rotavirus immunization might reduce overall diarrhoea morbidity by 2–3% and diarrhoea mortality by 6–10% among children under 5 years of age in developing countries.

The impact of improved cholera vaccines depends on the prominence of cholera as a cause of diarrhoea and this varies greatly from country to country. Taking the extreme example of Bangladesh, where cholera may account for about 0.4% of all diarrhoea episodes and 8% of all diarrhoea deaths in children under 5 years of age, cholera immunization might reduce overall diarrhoea morbidity by 0.06–0.13% and diarrhoea mortality by 1–2% among these children, based on various assumptions.

These vaccines are under development and vaccination schedules and delivery requirements are at present unknown. If an immunization programme can incorporate rotavirus vaccine at a marginal cost of US$ 2 (1982 prices) per fully immunized child, the likely cost-effectiveness values for the intervention are US$ 4 per diarrhoea case averted and US$ 312 per diarrhoea death averted in children under 5 years. For cholera immunization which may require additional immunization services at a cost of US$ 15 (1982 prices) per fully immunized child, the likely cost-effectiveness values are US$ 549 per diarrhoea case averted and US$ 10 714 per diarrhoea death averted in children under 5 years. These estimates are extremely tentative and are subject to revision as more is learnt about the epidemiology of rotavirus diarrhoea and cholera, and the features of immunization programmes against these diseases. In areas where more accurate epidemiological and economic data are available other estimates of cost-effectiveness can be computed.

The prominence of rotavirus diarrhoea in industrial countries, and the similar incidence rate in industrial and developing countries, suggest that rotavirus diarrhoea may not be controlled by improvements in water supply, sanitation, or hygiene. Control may depend upon the development, trial, and widespread use of an effective vaccine. It is hoped that rotavirus vaccine can be delivered within existing EPI programmes, and rotavirus immunization may prove to be a cost-effective intervention for national diarrhoeal diseases control programmes.

The cost-effectiveness of cholera immunization, as an intervention to reduce overall diarrhoea morbidity and mortality rates among young children, is more doubtful, even in Bangladesh, although it may have other applications. More data are required on vaccine efficacy and the duration of protection before firmer conclusions can be reached.

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RÉSUMÉ

INTERVENTIONS DANS LE CADRE DE LA LUTTE CONTRE LES MALADIES DIARRHÉIQUES DU JEUNE ENFANT: VACCINATION ANTICHOLÉRIQUE ET VACCINATION CONTRE LES ROTAVIRUS

Cet article est le septième d'une série d'études concernant les interventions susceptibles de réduire la morbidité et la mortalité imputables aux maladies diarrhéiques chez les enfants de moins de cinq ans dans les pays en développement. Nous avons étudié les effets potentiels de la vaccination contre les rotavirus et de la vaccination anticholérique (à l'aide d'un vaccin amélioré) sur la morbidité et la mortalité diarrhéiques, en utilisant des données provenant d'enquêtes de terrain et de calculs théoriques. Dans les pays en développement, les rotavirus sont probablement responsables d'environ 6% de tous les épisodes morbides et de 20% de l'ensemble des décès d'origine diarrhéique chez les enfants de moins de cinq ans. Ces proportions sont peut être plus élevées dans les pays industriels. Les effets potentiels d'une immunisation à l'égard des rotavirus sur le taux général d'atteinte diarrhéique chez les enfants de moins de cinq ans dépendra de l'âge auquel se pratique la vaccination, de l'efficacité du vaccin utilisé et de la couverture assurée par le programme. Avec un vaccin efficace à 80% et un taux de couverture de l'ordre de 45 à 75%, une vaccination contre les rotavirus pratiquée à l'âge de six mois peut diminuer les taux de mortalité diarrhéique de 1,8 à 3,0% et les taux de mortalité de 6 à 10%. Si cette vaccination est pratiquée à un âge moins avancé, par exemple trois mois, le gain sur cette

baisse des taux peut n'avoir qu'une importance marginale: 1,9–3,3% pour la morbidité et 6–11% pour la mortalité.

Les effets d'une amélioration des vaccins anticholériques dépendent du rôle prépondérant du choléra en tant que cause des maladies diarrhéiques — rôle qui varie considérablement d'un pays à l'autre. Au Bangladesh, le choléra est probablement responsable d'environ 0,4% de l'ensemble de la morbidité diarrhéique et de 8% de la totalité des décès d'enfants de moins de cinq ans imputables à ces maladies. Dans le cas particulier, on a suppose que le nouveau vaccin anticholérique était efficace à 70%. Le schéma d'administration utilisé pour ce nouveau vaccin est actuellement inconnu. Lorsqu'un nouveau vaccin ne confère pas de protection durable, l'âge optimal pour son administration se situe aux alentours de 24 mois, c'est-à-dire avant l'apparition du pic d'incidence cholérique spécifique pour cette classe d'âge. En pareil cas, le vaccin ne sera pas administré dans le cadre du PEV existant et, de la sorte, la couverture sera peut-être faible. Avec un vaccin efficace à 70% et un taux de couverture de l'ordre de 30 à 60%, la vaccination anticholérique pratiquée à l'âge de deux ans au Bangladesh pourrait diminuer les taux de morbidité diarrhéique de 0,06 à 0,13% et les taux de mortalité de 0,8 à 1,7%. Si la vaccination anticholérique est pratiquée à un âge moins avancé, par exemple six mois, et si par conséquent une meilleure couverture peut être assurée (45–75%), la réduction potentielle serait de l'ordre de 0,11 à 0,19% pour la morbidité diarrhéique et de 2,1 à 3,4% pour la mortalité.

S'il est possible d'englober dans un programme de vaccination une immunisation à l'égard des rotavirus moyennant un coût marginal de US$2 (prix de 1982) pour la vaccination complète de chaque enfant, le rapport coût-efficacité de cette intervention sera de l'ordre de US$4 pour chaque cas de maladie diarrhéique qu'il a été ainsi possible de prévenir, et de US$312 par décès évité chez les enfants de moins de cinq ans. Pour une vaccination anticholérique qui peut exiger un renforcement des services de vaccination d'un coût s'élevant à US$15 (prix de 1982) pour la vaccination complète de chaque enfant, le rapport coût-efficacité au Bangladesh sera vraisemblablement de US$549 pour chaque cas de maladies diarrhéiques qu'il sera possible de prévenir et de US$10 714 pour chaque décès évité chez les enfants de moins de cinq ans.

L'importance des maladies diarrhéiques à rotavirus dans les pays industriels, et l'analogie de leur taux d'incidence entre pays industriels et pays en développement, suggèrent qu'une amélioration des approvisionnements en eau, de l'assainissement ou de l'hygiène ne suffit peut-être pas pour juguler les affections de ce type. Leur maîtrise dépend sans doute de l'élaboration, de l'essai et de l'utilisation généralisée d'un vaccin efficace. Il est permis de penser qu'un vaccin contre les rotavirus pourrait être administré dans le cadre du Programme élargi de Vaccination et que cette intervention se révélera interessante, sur le plan du rapport coût-efficacité, pour les programmes nationaux de lutte contre les maladies diarrhéiques. La vaccination anticholérique, en revanche, peut exiger un renforcement des services de vaccination entraînant des coûts élevés pour un faible taux de couverture. Même au Bangladesh, le rapport coût-efficacite des interventions en faveur d'une diminution de la morbidité et de la mortalité diarrhéiques chez les jeunes enfants ne sera peut-être pas positif, bien que d'autres applications puissent être envisagées dans ce cadre.

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